Clinical Pharmacology BLA Review

Division of Clinical Evaluation and Pharmacology/Toxicology

Office of Tissues and Advanced Therapy

BLA	125771/0
Product	ALTUVIIIO (efanesoctocog alfa, BIVV001, rFVIIIFc-VWF-XTEN) lyophilized powder for reconstitution
Sponsor	Bioverativ Therapeutics Inc.
Indication	Treatment of hemophilia A
Date Received	June 30, 2022
Reviewer	Xiaofei Wang, Ph.D. Clinical Pharmacology Reviewer, General Medicine Branch 2 Division of Clinical Evaluation and Pharmacology/Toxicology
RPM	Niloofar Kennedy
Through	Tejashri Purohit-Sheth, M.D., FACAAI, CQIA Director Division of Clinical Evaluation and Pharmacology/Toxicology

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Table of Contents

1 EXECUTIVE SUMMARY

Bioverativ Therapeutics, Inc. seeks approval of its BLA for ALTUVIIIO (efanesoctocog alfa, BIVV001, rFVIIIFc-VWF-XTEN) for the treatment of hemophilia A in adult and children. ALTUVIIIO is a recombinant fusion protein consisting of a single chain B domain deleted human FVIII covalently linked to the D'D3 domain of human VWF via the Fc domain of human immunoglobulin G1 (IgG1) and 2 XTEN polypeptides. ALTUVIIIO is sterile, lyophilized powder for reconstitution for intravenous injection. The proposed dose of ALTUVIIIO for routine prophylaxis is 50 IU/kg once weekly via intravenous (IV) injection.

The clinical pharmacology evaluation of this biologics license application (BLA) is based on data from 6 clinical studies that enrolled previously treated patients (PTPs) with severe hemophilia A, and supportive population pharmacokinetic (popPK), population pharmacokinetic/ pharmacodynamic (PK/PD), and physiologically based PK (PBPK) analyses. After IV injection, the PK profile of ALTUVIIIO exhibited a shallow distribution phase followed by a linear, and non-saturable elimination phase with a long half-life compared to other approved FVIII products. Dose proportionality was observed for Cmax and AUC with doses ranging from 25 IU/kg to 65 IU/kg. Weekly dosing of 50 IU/kg of ALTUVIIIO showed minimal accumulation. With once weekly dose at 50 IU/kg, ALTUVIIIO provided FVIII activity in the normal to near-normal range (> 40 IU/dL) for 3 to 4 days and > 10 IU/dL at the end of the weekly dosing interval in adults and adolescents. Body weight was a statistically significant covariate on both clearance (CL) and volume of distribution (V). Younger children (< 12 years) with lower body weight had higher clearance, shorter half-life and lower Ctrough level of FVIII activity at steady state compared to adults and adolescents. Once weekly dose of ALTUVIIIO at 50 IU/kg provided FVIII activity in the normal to near-normal range (> 40 IU/dL) for 2 to 3 days, >10 IU/dL for approximately 6 to 7 days, and in the mild hemophilia range (>5 IU/dL) at the end of the weekly dosing interval in both cohorts of children <12 years of age. Despite the lower exposure, the interim efficacy results of the ongoing XTEND-Kids study showed that pediatric subjects with severe hemophilia treated with ALTUVIIIO had a comparable annual bleeding rate (ABR) to that observed in adults and adolescents despite a reduced FVIII activity level. In addition, results from population PK/PD analyses provided additional support for the dose of ALTUVIIIO at 50 IU/kg once weekly: the bleeding prevention in pediatrics younger than 12 years is predicted to be better than the efficacy of approved FVIII product, Eloctate in adults.

The proposed dosing regimen of ALTUVIIIO administered by intravenous (IV) injection has demonstrated clinical efficacy with a tolerable safety profile; therefore, the proposed dosing regimen is acceptable. From clinical pharmacology standpoint, the BLA is acceptable to support approval.

2 INTRODUCTION

ALTUVIIIO (efanesoctocog alfa, BIVV001, rFVIIIFc-VWF-XTEN)[1] is a long-acting recombinant fusion protein developed for the treatment of hemophilia A in adult and children. BIVV001 is a factor VIII replacement product that is designed to be independent of endogenous VWF in order to overcome the half-life limit imposed by FVIII and VWF interactions. BIVV001 is a recombinant fusion protein consisting of a single chain B domain deleted human FVIII covalently linked to the D'D3 domain of human VWF via the Fc domain of human immunoglobulin G1 (IgG1) and 2 XTEN polypeptides. XTEN peptides are unstructured hydrophilic polypeptides, composed of repeating motifs of 6 natural amino acids [Glycine, Alanine, Proline, Glutamic acid, Serine and Threonine].

In BIVV001, the first XTEN polypeptide is inserted in between FVIII N745 and E1649 amino acid residues, replacing the natural FVIII B domain. Thus, it is flanked by natural FVIII thrombin cleavage sites (b) (4), resulting in its release upon BIVV001 thrombin activation. The second XTEN polypeptide is inserted in between the D'D3 and Fc (fragment crystallizable region of IgG1). (b) (4)

(b) (4)

BIVV001 is a sterile, non-pyrogenic, lyophilized white to off-white cake powder for reconstitution for intravenous injection and is supplied in a single-use vial. The proposed dose of BIVV001 for routine prophylaxis is 50 IU/kg once weekly.

[1] In this review, ALTUVIIIO is also referred to as BIVV001.

This clinical pharmacology section of this application is supported by 6 clinical studies that enrolled previously treated patients (PTPs) with severe hemophilia A. To support its application, the applicant conducted population pharmacokinetic (PK) and population PK/pharmacodynamic (PD) analyses to evaluate the relationship between FVIII activity and bleed hazard. Physiologically based PK (PBPK) modeling was used to understand the effect of age ontogeny on BIVV001 PK profile and to further support pediatric dose selection of BIVV001. (Table 1)

3 SUMMARY OF IMPORTANT CLINICAL PHARMACOLOGY FINDINGS

BIVV001 is a recombinant fusion protein consisting of a single chain B domain deleted human FVIII covalently linked to the D'D3 domain of human VWF via the Fc domain of human immunoglobulin G1 (IgG1) and 2 XTEN polypeptides). BIVV001 is independent of endogenous VWF in order to overcome the half-life limit imposed by FVIII and VWF interactions.

General PK Profile: after administration via IV injection, the PK profile of BIVV001 exhibited a shallow distribution phase followed by a linear, and non-saturable elimination phase with a long half-life compared to other approved FVIII products. The mean terminal plasma half-life of BIVV001 was about 3.8- and 2.7-fold times the half-life of Advate (an approved FVIII product with standard half-life) and Adynovi (an approved FVIII product with extended half-life), respectively.

Dose proportionality: dose proportionality was observed for Cmax and AUC with doses ranging from 25 IU/kg to 65 IU/kg.

Steady State: weekly dosing of 50 IU/kg of BIVV001 showed minimal accumulation. With once weekly dose at 50 IU/kg, BIVV001 provided FVIII activity in the normal to near-normal range (> 40 IU/dL) for 3 to 4 days and > 10 IU/dL at the end of the weekly dosing interval in adults and adolescents. Once weekly dose of ALTUVIIIO at 50 IU/kg provided FVIII activity in the normal to near-normal range (> 40 IU/dL) for 2 to 3 days, >10 IU/dL for approximately 6 to 7 days, and in the mild hemophilia range (>5 IU/dL) at the end of the weekly dosing interval in both cohorts of children <12 years of age.

Intrinsic Factors Impacting BIVV001 PK Profiles (PK in Special Populations): Body weight was a statistically significant covariate on both clearance (CL) and volume of distribution (V). Younger children (< 12 years) with lower body weight had higher clearance, shorter half-life and lower Ctrough level of FVIII activity at steady state compared to adults and adolescents. In addition to body weight, Asian race was the only covariate that influenced the PK of BIVV001, with a higher C_{maxss}, C_{trough}, and time to 40 IU/dL FVIII activity in the Asian population compared to the non-Asian population. The PK differences between Asian and non-Asian population was

not considered clinically meaningful. Other covariates (VWF antigen levels, hematocrit, blood type, and HCV/HIV status) had no impact on BIVV001 PK profiles.

PK/PD Relationships: The relationship between FVIII activity level and bleeding prevention (clinical efficacy outcome) were evaluated using a repeated time-to-event (RTTE) model. Based on FVIII PK/PD analyses, the risk of bleeding is negatively correlated with FVIII activity. Once weekly 50 IU/kg BIVV001 provided factor VIII activity levels that were associated with a low bleed risk.

Adults and Adolescents: the probability of zero bleeds in 1 year with BIVV001 50 IU/kg once-weekly regimen was predicted to be 71% (95% CI: 50%-83%) in adults and adolescents, indicating a low risk of bleed for BIVV001. The probability of first bleed in 1 year with BIVV001 50 IU/kg once weekly regimen in adults and adolescents was 35% lower compared to label-recommended regimen (standard-of-care) of Eloctate (50 IU/kg every 4 days).

Pediatrics < 12 years: the probabilities of first bleed in 1 year were predicted to be 45% [95% CI: 39%-50%] and 48% [95% CI: 42%-54%] for pediatrics 6-<12 years and <6 years, respectively. 1.28 (±2.46). The predicted ABR in pediatrics treated with 50 IU/kg BIVV001 once weekly was 1.28, which was lower than ABR in in adult subjects with severe hemophilia A treated with 50 IU/kg Eloctate every 4 days (1.6). Additionally, despite the lower exposure, the interim efficacy results of the ongoing XTEND-Kids study showed that pediatric subjects with severe hemophilia treated with BIVV001 had a comparable annual bleeding rate (ABR) to that observed in adults and adolescents despite a reduced FVIII activity.

Above results indicates that BIVV001 the proposed dosing regimen of BIVV001 (50 IU/kg once weekly) is acceptable.

Immunogenicity: BIVV001 showed a low immunogenic potential in previously treated patients (PTPs) with hemophilia A. Inhibitor development to FVIII was not detected, and the incidence of treatment-emergent anti-drug antibodies (ADAs) was low: 4 out of 277 (2.2%) BIVV001 treated subjects developed transient ADAs. Factor VIII activity profiles of the 4 subjects with treatment emergent (TE) ADAs in Study EFC16293 overlapped with the factor VIII activity profiles of subjects with ADA negative profiles and their PK parameters were comparable to the mean of ADA negative subjects. No apparent differences with respect to bleeding episodes and the PD response after BIVV001 treatment were observed in the 4 subjects with treatment-emergent ADAs compared to ADA negative subjects. Available data indicates that there is no evident impact of ADAs on FVIII PK and clinical outcomes.

4 LABELING COMMENTS

The clinical pharmacology reviewer has reviewed the package insert for BLA 125771 and finds it acceptable pending the following revisions shown below.

12. CLINICAL PHARMACOLOGY

12.1. Mechanism of Action

ALTUVIIIO [antihemophilic factor (recombinant), Fc-VWF-XTEN fusion protein] ~~or recombinant coagulation factor VIII Fc Von Willebrand Factor XTEN fusion protein (rFIIIFc-VWF-XTEN) is a recombinant fusion protein that~~ temporarily replaces the missing coagulation factor VIII needed for effective hemostasis. ALTUVIIIO has demonstrated 3- to 4- fold prolonged half-life relative to other standard and extended half-life FVIII products ~~molecules~~.

Mechanism of Half-life Extension

ALTUVIIIO is a recombinant FVIII analogue fusion protein that is ~~designed to be~~ independent of endogenous VWF in order to overcome the half-life limit imposed by FVIII-VWF interactions. The D'D3 domain of VWF is the region that interacts with FVIII. Appending the D'D3 domain of VWF to a recombinant FVIII-Fc fusion protein provides protection and stability to FVIII and prevents FVIII interaction with endogenous VWF, thus overcoming the limitation on FVIII half-life imposed by VWF clearance.

The Fc region of human immunoglobulin G1 (IgG1) binds to the neonatal Fc receptor (FcRn). FcRn is part of a naturally occurring pathway that delays lysosomal degradation of immunoglobulins by recycling them back into circulation, ~~and~~ thus prolonging the plasma half-life of the fusion protein.

ALTUVIIIO contains 2 XTEN polypeptides, which alter the hydrodynamic radius of the fusion protein, thus reducing rates of clearance and degradation, and improving pharmacokinetic properties ~~further increase its PK~~. In ALTUVIIIO, the natural FVIII B domain (except 5 amino acids) is replaced with the first XTEN, inserted in between FVIII N745 and E1649 amino acid residues; and the second XTEN is inserted in between the D'D3 domain and Fc.

12.2. Pharmacodynamics

Hemophilia A is a bleeding disorder characterized by a deficiency of functional coagulation factor VIII (FVIII), which leads to a prolonged clotting time in the activated partial thromboplastin time (aPTT)-based one-stage clotting assay. Administration of ALTUVIIIO increases plasma levels of FVIII, temporarily correcting the coagulation defect in hemophilia A patients.

Based on FVIII pharmacokinetic/pharmacodynamic ~~exposure response~~ analyses, the risk of

bleeding is negatively correlated with FVIII activity. ~~in a typical patient with ALTUVIIIO 50 IU/kg once weekly regimen, the probability of zero bleed in 1 year was predicted to be 71% (95% CI: 50% 83%). The exposure response analyses, along with the clinical efficacy data in adult and adolescent patients with severe hemophilia supported ALTUVIIIO superior clinical efficacy profile compared to existing FVIII products *[see Clinical Studies (14)]*.~~

Comment to Applicant:
In subsection 12.3 Pharmacokinetics (PK), avoid using research terminology such as "Phase 1/2a" or "Phase 3." Also, avoid using study names, which may decrease readability. Simply describe each study. Additionally, there is a comparative PK study of other factor VIII products. Comparisons of the PK of other products should not be in the instructions for the safe and effective of ALTUVIIIO.

12.3. Pharmacokinetics

The PK of ALTUVIIIO were evaluated in the Phase 3 studies XTEND-1 and XTEND-Kids, enrolling 159 adults and adolescents, and 67 children <12 years old, respectively, receiving weekly IV injection of 50 IU/kg. Among children <12 years old, 32 subjects had ALTUVIIIO single dose PK profiles available.

PK parameters following a single dose of ALTUVIIIO are presented in Table 4. The PK parameters were based on plasma FVIII activity measured by the aPTT-based one-stage clotting assay. After a single dose of 50 IU/kg, ALTUVIIIO exhibited high sustained FVIII activity with prolonged half-life across age cohorts. There was a trend of increasing AUC, and decreasing clearance, with increasing age in the pediatric cohorts. The PK profile at steady state (Week 26) was comparable with the PK profile obtained after the first dose.

Table 4: Pharmacokinetic Parameters Following a Single Dose of ALTUVIIIO by age (one-stage clotting assay)

PK Parameters (mean SD)	Pediatric Study		Adult and Adolescent Study	
	1 to <6 Years N = 14	6 to <12 Years N = 18	12 to <18 years N = 25	Adults N = 134
AUC (IU*h/dL)	6710 (1190)	7190 (1450)	8350 (1550)	9850 (2010)[†]
$t_{1/2}$ (h)	39.9 (5.71)	42.4 (3.70)	44.6 (4.99)	48.2 (9.31)
CL (mL/h/kg)	0.740 (0.128)	0.681 (0.139)	0.582 (0.115)	0.493 (0.121)[†]

V_{ss} (mL/kg)	38.0 (7.19)	38.1 (6.80)	34.9 (7.38)	31.0 (7.32)†
MRT (hr)	51.9 (9.06)	56.3 (5.10)	60.0 (5.54)	63.9 (10.2)†

$AUC_{0\text{-}tau}$ = area under the activity-time curve over the dosing interval, CL = clearance, MRT = mean residence time, SD = standard deviation, $t_{1/2z}$ = terminal half-life, V_{ss} = volume of distribution at steady state.

† Calculation based on 128 profiles.

Comment to Applicant:

For consistency in describing FVIII activity between adults/adolescents and kids, please provide % of patients > 10 IU/dL in a similar manner for children.

Time above a FVIII target in pediatrics is already included in the table and the sentence is not necessary.

In XTEND-1, ALTUVIIIO at steady state maintained normal to near normal (>40 IU/dL) FVIII activity for a mean (SD) of 4.1 (0.7) days with once weekly prophylaxis in adults. The FVIII activity over 10 IU/dL was maintained in 83.5% of adults and adolescent subjects throughout the study. In children <12 years ALTUVIIIO maintained normal to near normal (>40 IU/dL) FVIII activity for 2 to 3 days and >10 IU/dL FVIII activity for approximately 6 to 7 days. The majority of children <12 years maintained FVIII activity in mild hemophilia range (>5 IU/dL) 7 days after the dosing (see Table 5).

Comment to Applicant:

Please add a row for "time to 20 IU/dL" to Table 5.

Table 5: Pharmacokinetic Parameters at Steady State of ALTUVIIIO by age (one-stage clotting assay)

PK Parameters Mean (SD)	**Pediatric Study†**		**Adult and Adolescent Study†**	
	1 to <6 years	**6 to <12 years**	**12 to <18 years**	**Adults**
	N = 20	**N = 35**	**N = 24**	**N = 124**
Peak (IU/dL)	113 (26.2)	121 (25.31)	124 (31.2)	150 (35.0)
IR (kg*IU/dL/IU)	2.10 (0.53)	2.17 (0.46)	2.25 (0.61)	2.64 (0.61)
Time to 40 IU/dL (h)‡	59.2 (7.68)	72.2 (11.2)	81.7 (13.1)	97.0 (20.2)
Time to 10 IU/dL (h)‡	139 (11.7)	163 (17.1)	179 (21.4)	200 (35.4)
Trough (IU/dL)	6.75 (2.29)	9.77 (3.64)	9.23 (4.77)	18.0 (16.6)

Peak = 15 min post dose at steady state, IR = incremental recovery, Trough – predose FVIII activity value at steady state, SD = standard deviation.

† Steady state peak, trough and IR were computed using available measurements at week 4 and week 52/End of study PK sampling visit for pediatric (XTEND-Kids) and adult and adolescent (XTEND-1) studies, respectively.

‡ Time to FVIII activity was predicted using population PK model.

Comment to Applicant:
Comparisons of the PK of other products should not be in the instructions for the safe and effective of ALTUVIIIO. Please remove this section. PK parameters of BIVV001 in Table 4 & 5 is sufficient to dosing recommendations.

~~Comparative Pharmacokinetics Study~~
~~In a Phase 1 PK study (PKM17085), the pharmacokinetic profiles of ALTUVIIIO, standard half-life (SHL) and extended half-life (EHL) recombinant FVIII products were evaluated after sequential IV injections in 13 male, previously treated patients, 18 to 65 years of age, with severe hemophilia A (defined as <1 IU/dL [<1%] endogenous FVIII). The terminal plasma half-life of ALTUVIIIO when compared against a currently marketed SHL and EHL recombinant Factor VIII (ADVATE® [Antihemophilic Factor (Recombinant)] and ADYNOVATE® [Antihemophilic Factor (Recombinant), PEGylated], respectively) was 3.94 and 2.82 fold longer (see Table 6).~~

~~Table 6: Comparison of ADVATE, ADYNOVATE, and ALTUVIIIO Pharmacokinetic Parameters Based on One-stage aPTT Clotting Assay~~

~~Parameter~~	~~Comparison~~	~~Point Estimate~~	~~90% CI~~
~~$t_{1/2z}$ (h)~~	~~ALTUVIIIO vs ADVATE~~	~~3.94~~	~~(3.47 to 4.48)~~
	~~ALTUVIIIO vs ADYNOVATE~~	~~2.82~~	~~(2.48 to 3.20)~~
~~AUC (h*IU/dL)~~	~~ALTUVIIIO vs ADVATE~~	~~6.03~~	~~(5.32 to 6.83)~~
	~~ALTUVIIIO vs ADYNOVATE~~	~~3.57~~	~~(3.15 to 4.05)~~

~~$AUC_{0\ tau}$ = area under the activity time curve over the dosing interval, $t_{1/2z}$ = terminal half-life~~

Comment to Applicant:
Generally, we have specific populations, which describes the covariates evaluated using PPK. This may be a substitute of the current heading. In addition, because the difference in PK due to body weight is already covered in the table describing adults/peds, we recommend following:

Specific Populations

The following factors have no clinically meaningful effect on the pharmacokinetics of ALTUVIIIO: age (1.4 to 72 years), sex, race (White, Asian), VWF antigen activity (40 to 339 IU/dL), hematocrit level (28% to 57%), blood type, HCV status, or HIV status. Body weight

(12.5 to 133 kg) is expected to alter weight normalized clearance (dL/h/kg) by 79% to -18% compared to a typical patient.

Population Pharmacokinetics

A population PK (POP PK) model was developed based on FVIII activity data from 260 subjects of all ages (range 1.4 to 72 years old) weighing between 12.5 kg to 133 kg in five clinical studies (39 subjects in Phase 1/2a studies, 159 subjects in adult and adolescent study, and 61 subjects in pediatric study). The population estimate for the typical CL and steady-state volume of distribution of ALTUVIIIO are 0.433 dL/h and 30.2 dL, respectively.

In addition, the model was also used to predict PK profile for routine prophylaxis, in treatment of bleeding episodes and peri-operative management of ALTUVIIIO.

Comment to Applicant:
Please add language for subjects who had ADAs.

Preceding the presentation of the data, add the regulatory language regarding differences in assays. Describe additional immunogenicity data (e.g., duration of exposure, assay sampling time) on the clinically insignificant effect reported.

Please refer to FDA Guidance for Industry – Immunogenicity Information in Human Prescription Therapeutic Protein and Select Drug Product Labeling – Content and Format (Draft, February 2022) (https://www.fda.gov/media/155871/download) for detailed information.

12.6. Immunogenicity

All subjects were monitored for neutralizing antibodies (inhibitors) to Factor VIII in the clinical program. No subjects developed neutralizing antibodies to Factor VIII.

The detection of antibodies that are reactive to Factor VIII is highly dependent on many factors, including the sensitivity and specificity of the assay, sample handling, timing of sample collection, concomitant medications, and underlying disease. Therefore, it may be misleading to compare the incidence of antibodies to ALTUVIIIO with the incidence of antibodies to other Factor VIII products.

5 RECOMMENDATIONS

The clinical pharmacology information in this BLA is acceptable, provided that satisfactory agreement is reached between the sponsor and the FDA regarding the language in Section 12 of the package insert. Please refer to section 4 for detailed Labeling Recommendations.

6 COMPREHENSIVE CLINICAL PHARMACOLOGY REVIEW

6.1 Overview of Clinical Pharmacology Evaluation of BIVV001

The clinical pharmacology section of this BLA includes 6 clinical studies that enrolled previously treated patients (PTPs) with severe hemophilia A. The PK of BIVV001 has been characterized in adult and pediatric PTPs with severe hemophilia A across clinical studies. BIVV001 was administered IV as a single dose (25 and 65 IU/kg) or repeated doses for 4 weeks with once weekly regimen (50 and 65 IU/kg) in the Phase 1/2a studies and subsequently with 50 IU/kg once-weekly for up to 52 weeks in the Phase 3 studies. A dense PK sampling schedule was implemented in Phase 1/2a studies, while a combination of dense and sparse PK sampling schemes was used in the Phase 3 studies.

FVIII activity in the PK samples was measured by two assays: activated partial thromboplastin time (aPTT)-based one-stage clotting assay (OSC) and (b) (4) chromogenic (CS) assay. The OSC assay was also used for BIVV001 potency assessment and was the primary PK assay to support dose selection. The PK results in this review are based on the OSC assay unless otherwise stated. FVIII activity values measured by CS assay were higher than the OSC assay by approximately 2.5-fold (90% CI: 2.47-2.57). This could be explained by the difference between the molar specific activities when measured by the CS assay versus the OSC assay. BIVV001 contains a single-chain version of FVIII and a covalently attached VWF-D'D3 domain requiring 2 thrombin cleavages to activate, or by subtle differences in thrombin cleavage surrounding the XTEN polypeptide and/or dissociation of XTEN/D′D3. This in turn is affected by thrombin concentration in the system and thrombin incubation time before tenase complex assembly, resulting in prolonged clotting times in the OSC assay.

To support this application, the applicant conducted population pharmacokinetic (PK) and population PK/pharmacodynamic (PD) analyses to evaluate the relationship between FVIII activity and bleed hazard. Physiologically based PK (PBPK) modeling was used to understand the effect of age ontogeny on BIVV001 PK profile and to further support pediatric dose selection of BIVV001 (Table 1).

Table 1. Clinical studies with BIVV001 pharmacokinetic assessments and other analyses

Study type	Study code Phase	Number of participants enrolled	Treatment duration Dose	Clinical study completion
Pharmacokinetics and initial tolerability in patients with hemophilia A				
Single ascending dose	242HA101 (TDU16220) Phase 1/2a	16 (7 in the low dose cohort, 9 in the high dose cohort)	Single dose Low dose cohort: 25 IU/kg Advate®, then 25 IU/kg BIVV001 High dose cohort: 65 IU/kg Advate, then 65 IU/kg BIVV001	Completed
Multiple ascending doses study	242HA102 (TDR16219) Phase 1/2a	24 (10 in the 50 IU/kg cohort, 14 in the 65 IU/kg cohort)	4 once-weekly doses Cohort 1: 50 IU/kg BIVV001 Cohort 2: 65 IU/kg BIVV001	Completed
Sequential single dose study	PKM17085 Phase 1	13	Single dose 50 IU/kg Advate, then 50 IU/kg Adynovi®/Adynovate®, then 50 IU/kg BIVV001	Completed
Pharmacokinetics and initial tolerability in patients with von Willebrand disease				
Single dose study in Type 2N and 3 von Willebrand disease population	PKM16978 Phase 1	5[a]	Single dose 25 IU/kg BIVV001	Ongoing[b]
Efficacy and safety studies in patients with severe hemophilia A				
Safety, efficacy, and PK in patients ≥12 years of age	EFC16293 (XTEND-1) Phase 3	159 (133 in Arm A, 26 in Arm B)	Arm A (prophylaxis): 52 weeks 50 IU/kg BIVV001 once weekly Arm B: 26 weeks 50 IU/kg BIVV001 (on demand), then 26 weeks 50 IU/kg BIVV001 once weekly (prophylaxis)	Completed
Safety, efficacy, and PK in patients <12 years of age	EFC16295 (XTEND-kids) Phase 3	67 (31 in <6 years of age cohort, 36 in 6 to <12 years age cohort)[a]	52 weeks 50 IU/kg BIVV001 once weekly	Ongoing[c]
Long-term safety and efficacy in patients ≥12 years of age	LTS16294 (XTEND-ed) Phase 3	159 (123 in Arm A, 32 in Arm B, 4 in Arm C)[a]	Up to 4 years 50 IU/kg BIVV001 once weekly	Ongoing[d]

Study type	Study code Phase	Number of participants enrolled	Treatment duration Dose	Clinical study completion
Population PK analysis of BIVV001 using one-stage clotting (OSC) assay	POH0727	39	Includes data from studies 242HA101, 242HA102	Not applicable
Population PK analysis of BIVV001 using OSC assay	POH0731	260	Includes data from es 242HA101, 242HA102, EFC16293, EFC16295, LTS16294 Includes data from 998HA101, 997HA301 [A-LONG] and 8HA01EXT [ASPIRE] Eloctate studies	Not applicable
Physiologically based PK analysis	PBM0083	37 on BIVV001	Includes data from studies 242HA101, 242HA102	Not applicable
Population PK/PD analysis of BIVV001 using OSC assay and bleeding events	POH0989	159	Includes data from Study EFC16293	Not applicable
Population PK/PD analysis using bleeding event data for Eloctate[e]	POH0886	181	Includes data from 998HA101, 997HA301 [A-LONG] and 8HA01EXT [ASPIRE] Eloctate studies	Not applicable

OSC = one-stage clotting (assay); PD = pharmacodynamic; PK = pharmacokinetic.

Advate is a full length recombinant factor VIII, and Adynovi/Adynovate is a PEGylated full length recombinant factor VIII

a Study ongoing. Number of participants enrolled as of cut-off date (24 January 2022)

b No PK data from this study is included in this submission

c Interim results included in the current submission

d FVIII activity listing is included only for Arm C in the current submission

e Supportive PK/PD analysis with Eloctate (a fusion protein comprising a recombinant BDD factor VIII and an Fc from Sanofi/Sobi) using data from clinical studies included in the BLA125487 and subsequent submissions

Source: Applicant. Module 2, Section 2.7.2. Summary of Clinical Pharmacology Studies.

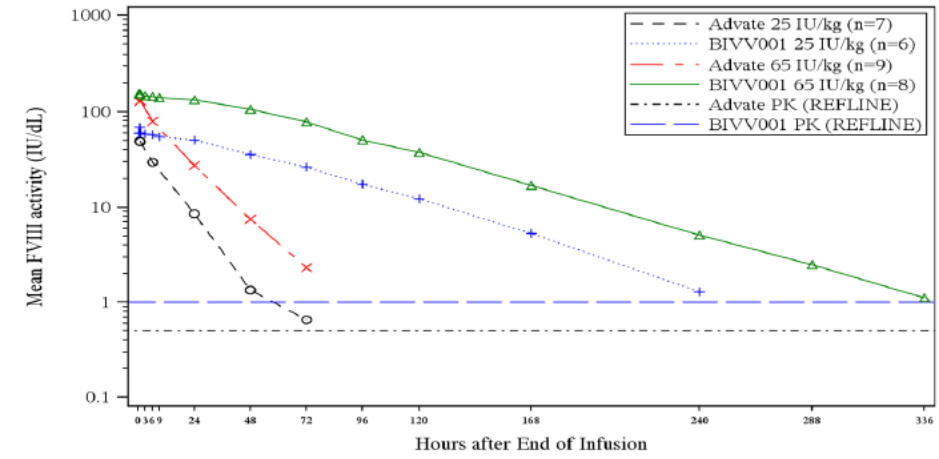
6.2 General Pharmacology and Pharmacokinetics

6.2.1 General Pharmacokinetic Profile

BIVV001 a recombinant fusion protein which is designed to be independent of endogenous VWF in order to overcome the half-life limit imposed by FVIII and VWF interactions. After IV injection, BIVV001 is primarily distributed in the circulatory system as illustrated by the limited volume of distribution. The clearance of BIVV001 is governed by 2 mechanisms: recycling

through FcRn and VWF-independent clearance, both of which would reduce the clearance and prolong the half-life compared to other FVIII products. The presence of 2 XTEN polypeptides further reduces the clearance. As shown in Figure 1, after administered via IV injection, the PK profile of BIVV001 exhibited a shallow distribution phase followed by a linear, and non-saturable elimination phase with a long half-life compared to other approved FVIII products.

Figure 1. Baseline-Corrected FVIII Activity (Mean) Over Time After a Single (or First) Dose of BIVV001 (Study 242HA101)



Note: REFLINE refers to lower limit of quantitation (LLOQ) which was <0.5 IU/dL for Advate and <1.0 IU/dL for BIVV001.
For the purpose of analysis, values below the LLOQ were treated as 0 IU/dL.

Source: Applicant. Section 2.7.2. Summary of Clinical Pharmacology Studies.

Table 2 summarizes PK parameters following a single (or first) dose of BIVV001. After a single (or first) dose of 50 IU/kg, BIVV001 showed high sustained FVIII activity with prolonged half-life across age cohorts. The mean half-life of BIVV001 ranged from 39.9 to 48.2 hours across different age groups. There was a trend of increasing AUC, and decreasing clearance, with increasing age in pediatric cohorts. The impact of age on BIVV001 PK profiles is discussed in detail in subsection 6.2.4 (PK in Special Populations) of this review.

Table 2. Pharmacokinetic Parameters for Baseline-corrected FVIII Activity Following a Single (or First) Dose of BIVV001 by Age

PK Parameters (mean SD)	Pediatric Study		Adult and Adolescent Study	
	1 to <6 Years N = 14	6 to <12 Years N = 18	12 to <18 years N = 25	Adults N = 134
AUC (IU*h/dL)	6710 (1190)	7190 (1450)	8350 (1550)	9850 (2010)†
$t_{1/2}$ (h)	39.9 (5.71)	42.4 (3.70)	44.6 (4.99)	48.2 (9.31)

CL (mL/h/kg)	0.740 (0.128)	0.681 (0.139)	0.582 (0.115)	0.493 (0.121)†
V_{ss} (mL/kg)	38.0 (7.19)	38.1 (6.80)	34.9 (7.38)	31.0 (7.32)†
MRT (hr)	51.9 (9.06)	56.3 (5.10)	60.0 (5.54)	63.9 (10.2)†

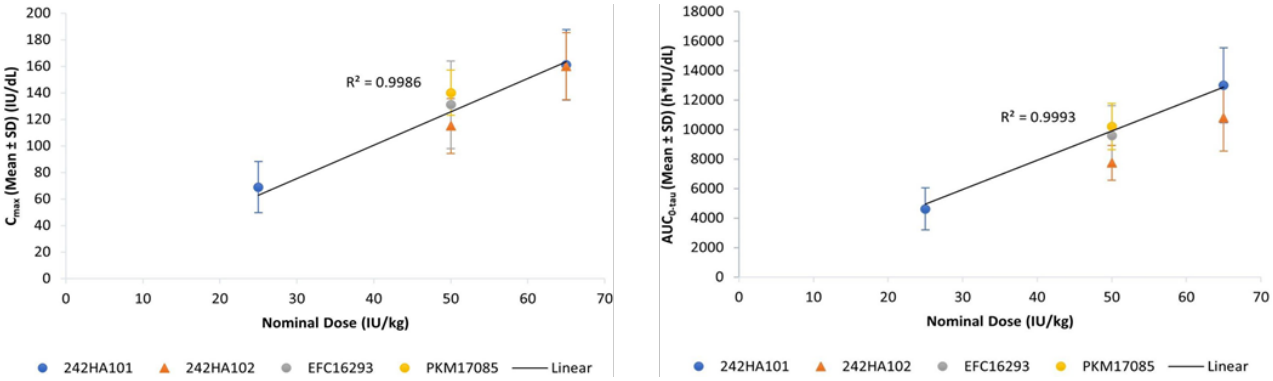
† Calculation based on 128 profiles.

Source: Applicant. Section 2.5. Clinical Overview.

6.2.2 Dose Proportionality

Following a single (or first) dose of BIVV001, dose proportionality was observed for Cmax and AUC (Figure 2). Table 3 summarizes the PK parameters of BIVV001 at the doses ranging from 25 to 65 IU/kg. The incremental recovery (IR) was consistent across the doses. The clearance (CL) and volume of distribution at steady state (Vss) were independent of dose between 25 and 65 IU/kg.

Figure 2. BIVV001 Cmax and AUC by Dose in Subjects with Hemophilia A After a Single (or First) Dose



For PKM17085 and 242HA101, numbers correspond to AUC

Source: Applicant. Section 2.7.2. Summary of Clinical Pharmacology Studies.

Table 3. BIVV001 Pharmacokinetic Parameters (baseline-corrected) after Single Dose on Day 1

Day 1 Mean (SD)	**25 IU/kg 242HA101** N=6	**50 IU/kg-242HA102** N=9	**50 IU/kg-EFC16293** N=159	**50 IU/kg-PKM17085** N=13	**65 IU/kg-242HA101** N=8	**65 IU/kg-242HA102** N=14
Cmax (IU/dL)	68.90 (19.2)	115 (20.7)	131 (33.0)	140 (16.9)	161 (26.6)	160 (25.2)
AUC0-tau (h*IU/dL)	4620 (1430)	7740 (1180)	9600 (2010) *b*	10200 (1560)	13000 (2540)	10800 (2260)
T1/2 (h)	37.81 (4.81)	Not determined	47.5 (8.86)	44.4 (10.4)	42.98 (3.65)	Not determined

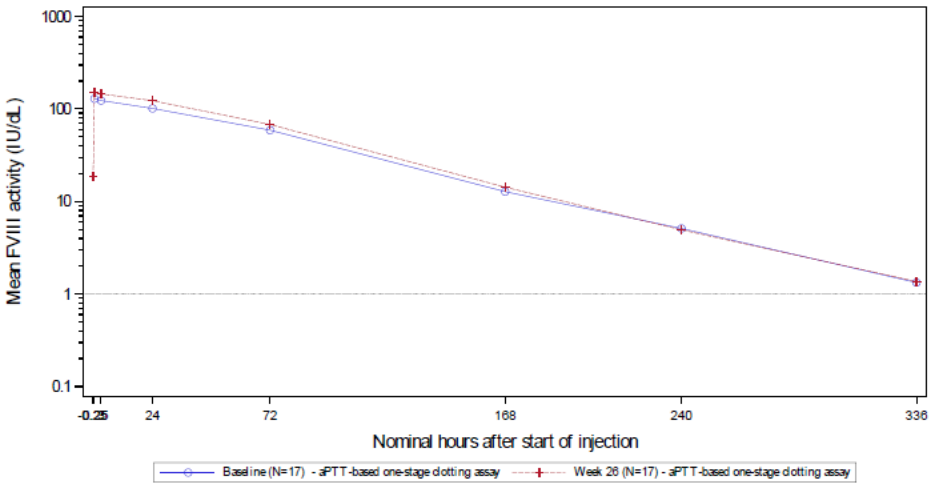
CL (mL/h/kg)	0.59 (0.22)	0.61 (0.11) *a*	0.51 (0.12) *b*	0.50 (0.10)	0.51 (0.10)	0.60 (0.14) *a*
Vss (mL/kg)	36.0 (9.87)	38.3 (8.31)	31.7 (7.44) *b*	31.3 (3.44)	36.3 (7.58)	34.8 (6.95)
IR (IU/dL per IU/kg)	2.76 (0.77)	2.29 (0.42)	2.60 (0.65)	2.80 (0.34)	2.48 (0.41)	2.46 (0.39)

CL = clearance; SD = standard deviation; V_{ss} = volume of distribution at steady state.
a Values from Day 22 after 4 weekly doses
b *n=153*
For PKM17085 and 242HA101, numbers correspond to AUC (area under the curve extrapolated to infinity)
Source: The reviewer compiled from Applicant submitted clinical studies in Module 5.

6.2.3 Pharmacokinetics at Steady State

As shown in Figure 3, the PK profiles of BIVV001 after a single dose and after multiple once-weekly doses were comparable in adults and adolescents with hemophilia A. Once-weekly dosing of BIVV001 at 50 or 65 IU/kg for 4 weeks (Study 242HA102) as well as at 50 IU/kg dosing for 26 weeks (Study EFC16293) resulted in minimal accumulation. BIVV001 showed comparable exposure (Cmax and AUC0-tau) at the same dose levels across studies.

Figure 3. Mean Baseline-Corrected FVIII Activity (mean) over Time After Administration of BIVV001 at 50 IU/kg (Study EFC16293) (OSC Assay)



Note: 1: For aPTT-based one-stage clotting assay, values below 1 IU/dL (i.e., LLOQ) are imputed as zero.
2: The horizontal dash line at y= 1 IU/dL represents LLOQ.
Source: Applicant. Section 2.7.2. Summary of Clinical Pharmacology Studies.

Table 4 summarized steady state FVIII activity in adult and pediatric subjects with hemophilia A treated with 50IU/kg BIVV001 once weekly. Due to higher clearance, the exposure of BIVV001 at steady state in pediatrics younger < 12 years of age was lower than that observed in adults and adolescents administered 50 IU/kg once weekly dose. The Cmax,ss and Ctrough,ss of BIVV001 were about 19-24% and 46-63% lower, respectively, in pediatrics < 12 years relative to adults.

BIVV001 at steady state maintained normal to near normal (>40 IU/dL) FVIII activity for a mean (SD) of 4.1 (0.7) days with once weekly prophylaxis in adults. The FVIII activity over 10 IU/dL was maintained in 83.5% of adults and adolescent subjects throughout the study. In children <12 years ALTUVIIIO maintained normal to near normal (>40 IU/dL) FVIII activity for 2 to 3 days and >10 IU/dL FVIII activity for approximately 6 to 7 days. The majority of children <12 years maintained FVIII activity in mild hemophilia range (>5 IU/dL) 7 days after the dosing (Table 4).

Table 4. Steady State FVIII Activity in Adults and Pediatrics Treated with 50 IU/kg BIVV001 once Weekly

PK Parameters	1 to <6 years	6 to <12 years	12 to <18 years	Adults
	N = 20	N = 35	N = 24	N = 124
Peak (IU/dL)	113 (26.2)	121 (25.31)	124 (31.2)	150 (35.0)
IR (kg*IU/dL/IU)	2.10 (0.53)	2.17 (0.46)	2.25 (0.61)	2.64 (0.61)
Trough (IU/dL)	6.75 (2.29)	9.77 (3.64)	9.23 (4.77)	18.0 (16.6)
Time to 40 IU/dL (h)	59.2 (7.68) [35%]	72.2 (11.2) [43%]	81.7 (13.1) [49%]	97.0 (20.2) [58%]
Time to 20 IU/dL (h)	99.3 (9.15) [59%]	117 (13.9) [70%]	130 (15.7) [77%]	150 (31) [89%]
Time to 10 IU/dL (h)	139 (11.7) [83%]	163 (17.1) [97%]	179 (21.4) [107%]	200 (35.4) [119%]

Note: Peak = 15 min post dose at steady state, IR = incremental recovery, Trough – predose FVIII activity value at steady state, SD = standard deviation.

- Steady state peak, trough and IR were computed using available measurements at week 4 and week 52/End of study PK sampling visit for pediatric (XTEND-Kids) and adult and adolescent (XTEND-1) studies, respectively. Values expressed as MEAN (SD).
- Time to FVIII activity was predicted using population PK model and values expressed as MEAN (SD) [Fraction of dosing interval].

Source: Applicant. Module 5, Applicant's PopPK report (Appendix 14) and clinical overview (Table 2).

6.2.4 PK in Special Populations

The applicant developed a population PK (PopPK) model using plasma one-stage FVIII activity data to assess sources of variability (intrinsic and extrinsic covariates) of BIVV001 in adult and pediatric patients with hemophilia A. To understand the effect of age ontogeny on BIVV001PK profile in younger subjects and further support pediatric dose selection, the applicant also developed physiologically based pharmacokinetic (PBPK) modeling with age ontogeny built in the model.

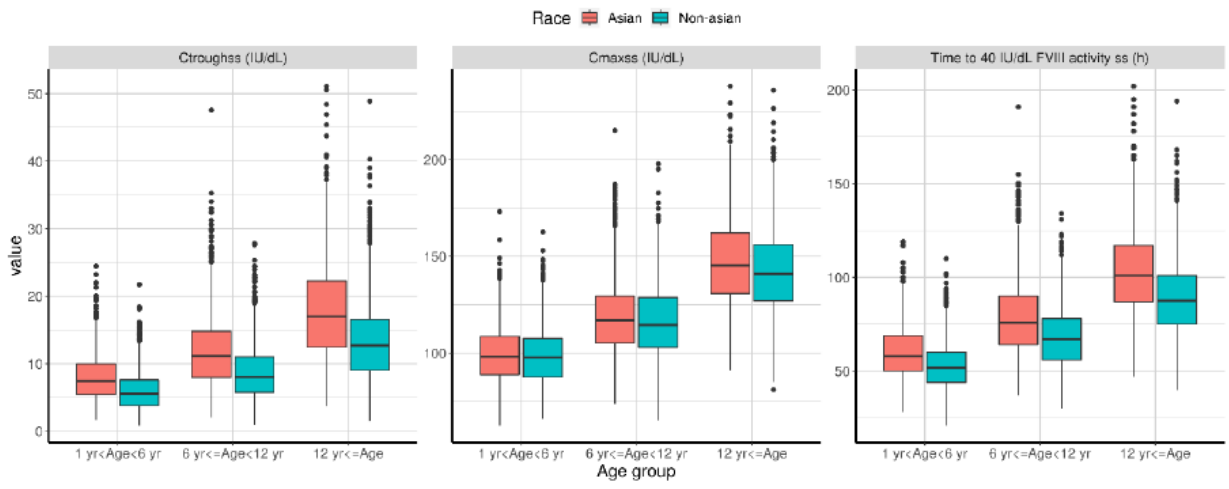
Results of PopPK analyses indicated that weight was a statistically significant covariate on both clearance (CL) and volume of distribution (V). Exposure of BIVV001 increased with increasing body weight. In pediatrics, weight grows congruently with age. Younger children with lower body weight had higher clearance and lower Ctrough level of FVIII activity at steady state compared to adults and adolescents. Simulation results suggested the overall exposure of

BIVV001 at steady state was lower in pediatrics <12 years than adolescents and adults receiving the same 50 IU/kg dose. The duration with FVIII activity above 10 IU/dL, 20 IU/dL, and 40 IU/dL was shorter in pediatrics <12 years, especially those <6 years (Figure 4). The steady state exposure of BIVV001 administered weekly in 32 pediatric (XTEND-Kids) and 149 adult (XTEND-1) patients was predicted based on post-hoc PK parameters from final PK model. All age group cohorts except pediatrics <6 years showed good agreement in PK parameter estimates between posthoc and NCA analyses. For pediatrics < 6 years, post-hoc Cmax was about 23% lower than observed Cmax, suggesting a mild age effect in young pediatrics on V (Table 5). This effect is not considered clinically meaningful as the annualized bleeding rates were not significantly impacted.

Asian race (N=40) was identified to have a reduced CL compared to other races including White (N=177), Black (N=5) and other/unreported (N=38). With lower clearance, Asian population had a higher Cmax,ss, Ctrough, and time to 40 IU/dL FVIII activity compared to non-Asian population. However, above difference was not considered clinically meaningful.

Other covariates such age, hepatitis C/HIV infection status, or blood type had no significant effect on BIVV001 PK (Figure 4). Please refer to Pharmacometrics Review for detailed information for PopPK and PBPK analysis.

Figure 4. Model Predicted Exposure of BIVV001 at Steady State by Age and Asian Race



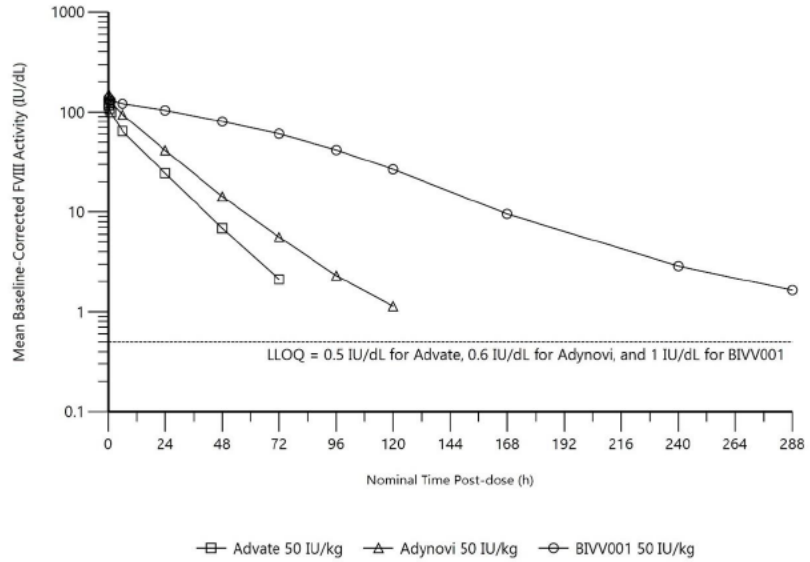
Source: Applicant. Module 5. Applicant's PopPK report.

6.2.5 PK Comparison to Other Approved FVIII Products

BIVV001 is a recombinant fusion protein that is designed to be independent of endogenous VWF in order to overcome the half-life limit imposed by FVIII and VWF interactions. In a Phase 1 open-label study (Study #PKM17085), the PK profiles of BIVV001, and two approved FVIII

products (Advate, a recombinant FVIII product with standard half-life, and Adynovi, a recombinant FVIII product with extended half-life) were evaluated after sequential injections in 13 male, adult previously treated patients with severe hemophilia A. The mean terminal plasma half-life of BIVV001 was about 3.8- and 2.7-fold times the half-life of Advate and Adynovi, respectively (Table 5 & Figure 5).

Figure 5. Mean Baseline-corrected FVIII Activity Over Time Following a Single Dose of Advate, Adynovi and BIVV001



Note: Mean baseline-corrected FVIII activity for BIVV001 was below lower limit of quantitation (LLOQ) by 336 hours (14 days) post-dose.
LLOQ was 0.5 IU/dL for Advate, 0.6 IU/dL for Adynovi, and 1 IU/dL for BIVV001.

Source: Applicant. Section 2.7.2. Summary of Clinical Pharmacology Studies.

Table 5. Summary of PK Parameters of Baseline-corrected FVIII Activity Following a Single Dose of Advate, Adynovi, and BIVV001

PK Parameters	Advate (Mean ± SD)	Adynovi (Mean ± SD)	BIVV001 (Mean ± SD)
n	13	13	13
C_{max} (IU/dL)	119 ± 14.7	151 ± 30.3	140 ± 16.9
IR (IU/dL per IU/kg)	2.37 ± 0.295	3.02 ± 0.605	2.80 ± 0.338
AUC (IU*h/dL)	1820 ± 748	2950 ± 905	10200 ± 1560
CL (mL/h/kg)	3.26 ± 1.48	1.86 ± 0.618	0.503 ± 0.0974
V_{ss} (mL/kg)	40.1 ± 6.82	34.5 ± 6.60	31.3 ± 3.44
$t_{1/2z}$ (h)	11.7 ± 4.55	16.3 ± 5.63	44.4 ± 10.4

Source: Applicant. Section 2.7.2. Summary of Clinical Pharmacology Studies.

6.3 Pharmacokinetic / Pharmacodynamic Relationships

One of the well-established clinical outcomes for assessment of efficacy of FVIII prophylaxis is annualized bleeding rate (ABR). Routine prophylaxis with standard half-life (SHL) and extended half-life (EHL) recombinant FVIII (rFVIII) products have demonstrated decreases in ABRs compared to on-demand treatment. To further understand and establish the relationship between FVIII activity levels and the subsequent risk of bleeding in patients with severe hemophilia A on FVIII prophylaxis, the applicant conducted pharmacokinetic/pharmacodynamic (PK/PD) analyses using a repeated time-to-event model (RTTE). The applicant conducted two RTTE analyses: the first using data from the Phase 3 study XTEND-1 (Study EFC 16295) for BIVV001 as primary analysis and the second using Eloctate clinical data as a supplemental analysis. The bleeding events in adult and adolescent study subjects dosed with BIVV001 were well described by a repeated time-to-event model (RTTE) whose base hazard was best characterized by a Weibull function. The base hazard was reduced by FVIII activity in an exposure dependent manner at the therapeutic range.

Table 6 shows the predicted probability in 1 year in a typical hemophilia A patient and ABR in a virtual population for BIVV001 and Eloctate with continuous infusion regimens to maintain FVIII activity at certain levels. When steady-state FVIII activity maintained at constant levels increases between 20 IU/dL to 40 IU/dL, the probability of a first bleed in 1 year and ABR decreases for both BIVV001 and Eloctate. The probability of first bleed in 1 year and ABR are comparable between Eloctate and BIVV001 at a given constant FVIII level. However, Eloctate would need to be administered at ~4-fold higher weekly dose than BIVV001 in order to achieve similar constant FVIII levels.

Table 6. Probability of First Bleed in 1 Year in a Typical Patient and Annualized Bleeding Rate (ABR) in Virtual Population for BIVV001 and Eloctate for Continuous Infusion Regimens that Maintain FVIII Activity at 20 IU/dL, 25 IU/dL, 30 IU/dL, 35 IU/dL and 40 IU/dL[d]

Compound	Dosing regimen (IU/kg/week[a])	Constant FVIII activity at steady state (IU/dL)	Probability (%) of first bleed in 1 year (95% CI) in a typical patient[b]	Annualized bleed rate (ABR) in virtual population (N=1000)	
				Mean (SD[c])	Median (IQR[c])
BIVV001	18.6	20	45.0 (29.0, 68.0)	1.2 (2.4)	0 (0, 1)
	23.2	25	39.0 (24.0, 62.0)	0.99 (2.0)	0 (0, 1)
	27.9	30	34.0 (19.0, 56.0)	0.84 (1.6)	0 (0, 1)
	32.5	35	30.0 (16.0, 52.0)	0.64 (1.3)	0 (0, 1)
	37.2	40	27.0 (14.0, 48.0)	0.66 (1.4)	0 (0, 1)
Eloctate	79.9	20	48.0 (37.0, 60.0)	1.0 (1.7)	0 (0, 1)
	100	25	43.0 (32.0, 55.0)	0.86 (1.4)	0 (0, 1)
	119.9	30	38.0 (28.0, 50.0)	0.84 (1.5)	0 (0, 1)

	139.8	35	35.0 (24.0, 47.0)	0.65 (1.1)	0 (0, 1)
	159.8	40	32.0 (21.0, 44.0)	0.61 (1.1)	0 (0, 1)

[a] Drug was dosed as continuous infusion over 1 week.

[b] For BIVV001 the typical patient has bodyweight of 78.3 kg; for Eloctate the typical patient has bodyweight of 73 kg, VWF of 118 IU/dL and hematocrit of 45%.

[c] Simulated IQR is 25th percentile to 75th percentile. CI is confidence interval and SD is standard deviation

[d] The data needs careful interpretation as dosing regimen is hypothetical and doses simulated were not tested in the clinical studies.

Source: Applicant's IR response dated 11/18/2022 (Table 1).

Based on RTTE model simulations, the probability of zero bleeds in 1 year with BIVV001 50 IU/kg once-weekly regimen was predicted to be 71% (95% CI: 50%-83%), indicating a low risk of bleed with BIVV001. The probability of first bleed in 1 year with BIVV001 50 IU/kg once weekly regimen in adults and adolescents was 35% lower compared to label-recommended regimen (standard-of-care) of Eloctate (50 IU/kg every 4 days). The probability of first bleed in 1 year with BIVV001 50 IU/kg once weekly regimen was 35% lower compared to the hypothetical 10 IU/kg continuous infusion regimen that maintained FVIII activity stable at 10.8 IU/dL, thus highlighting the benefit of normal to near-normal FVIII levels (>40 IU/dL). With a hypothetical dose regimen of 50 IU/kg every 2 days of Eloctate, the bleeding probability was further reduced. However, this dosing regimen may not be ideal in clinical practice due to short dosing interval. For routine prophylaxis, BIVV001 of 50 IU/kg once weekly was expected to achieve similar efficacy as Eloctate of 50 IU/kg every 2 days (Table 7 & Figure 6).

Table 7. Comparison of Typical Patient Probability of First Bleed in 1 Year and FVIII Activity Metrics for BIVV001 and Eloctate

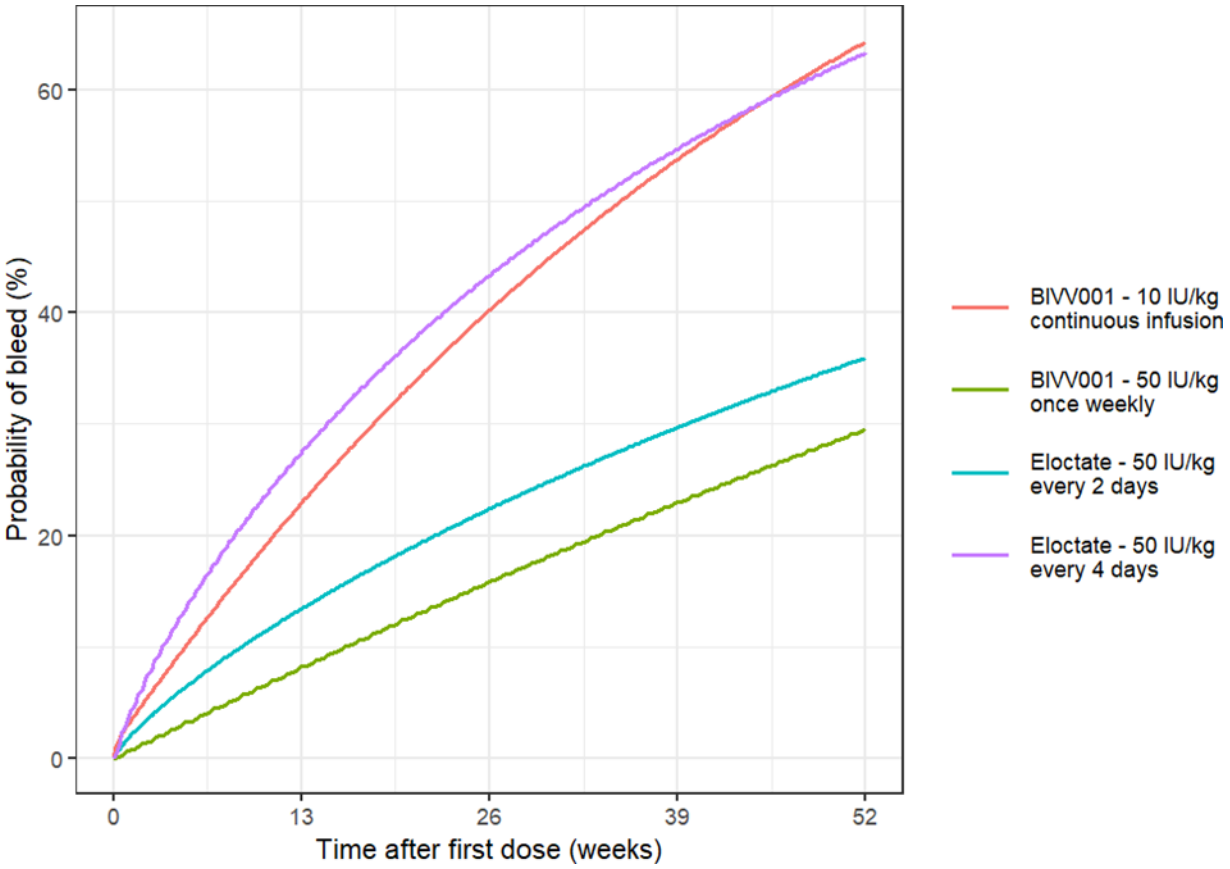
RTTE model	Regimen	Steady state FVIII C_{trough} (IU/dL)	Time >10 IU/dL FVIII (% of dosing interval)	Time >40 IU/dL FVIII (% of dosing interval)	Probability (%) of first bleed in 1 year (95% CI)
BIVV001[a]	50 IU/kg once weekly	12.8	100	52.6	29.0 (17.0-50.0)
	10 IU/kg continuous[c]	10.8	97.9	0.00	64.0 (44.0-84.0)
	12 IU/kg continuous[c]	12.9	98.8	0.00	58.0 (40.0-80.0)
	15 IU/kg continuous[c]	16.1	99.2	0.00	52.0 (35.0-74.0)
Eloctate[b]	50 IU/kg once every 4 days[d]	1.79	52.9	19.2	64.0 (52.0-74.0)
	50 IU/kg once every 2 days[e]	13.0	100	44.0	36.0 (26.0-47.0)

FVIII = coagulation factor VIII; CI = confidence interval; RTTE = repeated time to event.

a Typical patient for BIVV001 is a patient with a body weight of 78.3 kg
b Typical patient for Eloctate is a patient with a body weight of 73.0 kg, VWF of 118 IU/dL and hematocrit of 45%
c Hypothetical continuous infusion, where the dose is infused over 1 week, eg, for 10 IU/kg continuous infusion, for 78.3 kg patient, 783 IU are infused over 1 week and continued for 52 weeks. For continuous infusion regimens, the steady state FVIII C_{trough} is stable FVIII activity at steady state.
d Label-recommended dosing regimen in the US.
e Hypothetical dosing regimen.

Source: Applicant. Section 2.7.2. Summary of Clinical Pharmacology Studies.

Figure 6. Probability of First Bleed (%) with Time Over 52 Weeks for Various Dosing Regimens

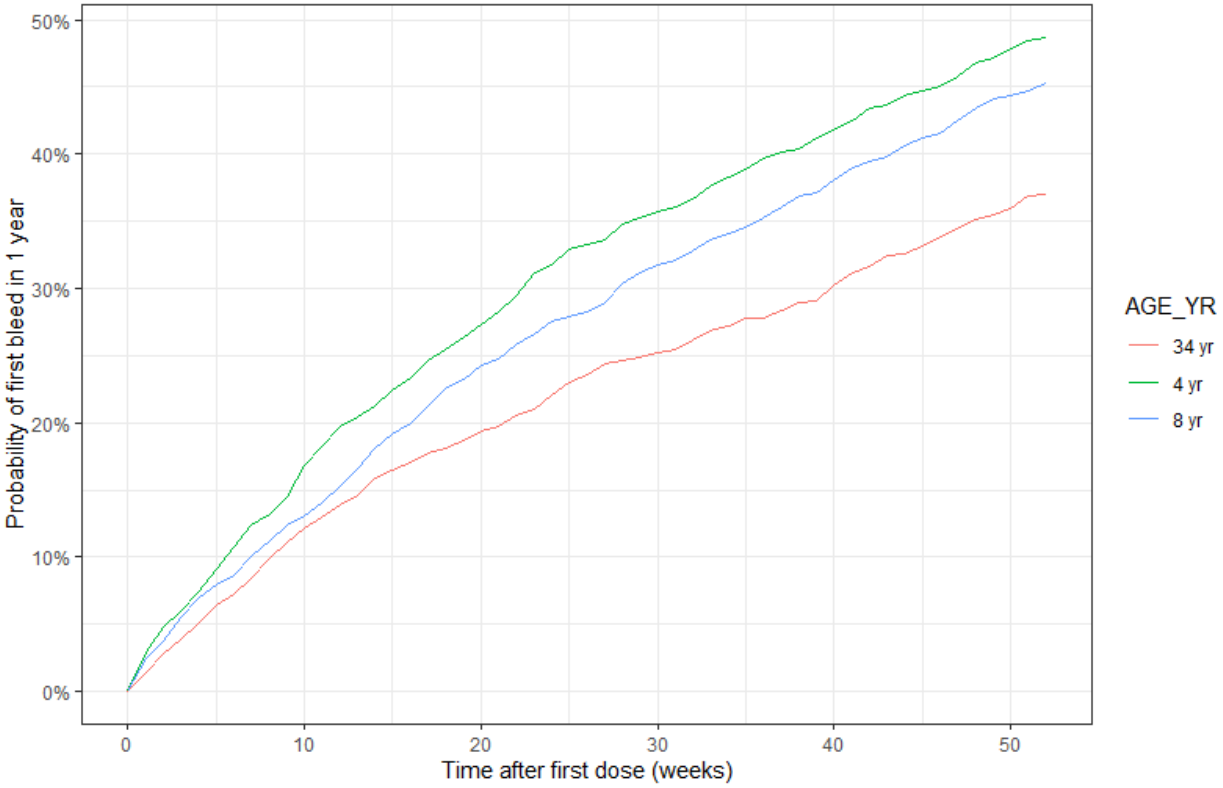


Source: Applicant. Section 2.7.2. Summary of Clinical Pharmacology Studies.

The efficacy impact of a reduced exposure in pediatrics was further evaluated with the RTTE model. Since the RTTE model was developed with adult and adolescent data, there is uncertainty of the PK/PD relationship in pediatric patients younger than 12 years. Therefore, the PK/PD analysis (extrapolation) in pediatrics was evaluated together with other clinical evidence to support the dose proposed for pediatric patients younger than 12 years. Based on simulations for the proposed prophylactic dosage (50 IU/kg BIVV001 once weekly) in typical subjects of different age cohorts using the RTTE model, the probabilities of first bleed in 1 year were predicted to be

45% [95% CI: 39%-50%] and 48% [95% CI: 42%-54%] for pediatrics 6-<12 years and <6 years, respectively (Figure 7).

Figure 7. Probability of First Bleed in 1 Year by Age Group



Source: FDA's analysis based on the RTTE model. The typical subject: adult and adolescent patient of 34 years weighing 78 kg, pediatric patient of 8 years weighing 33 kg for 6-<12 years age cohort, and pediatric patient of 4 years weighing 18 kg for <6 years age cohort. 1000 simulation per a typical subject was conducted with weekly intervals.

The bleeding risks were further compared between pediatric subjects with severe hemophilia A treated with BIVV001 at 50 IU/kg once weekly and adult subjects with severe hemophilia A treated with 50 IU/kg Eloctate every 4 days. The ABR in adults with severe hemophilia A treated with 50 IU/kg Eloctate every 4 days was 1.6. RTTE model and simulation was conducted for virtual patient population using National Health and Nutrition Examination Survey (NHANES) 2017-2020 pre-pandemic data. In pediatrics including age down to birth, the predicted ABRs were 0.97 (±1.69) and 1.37 (±2.46) in 6-<12 years and <6 years, respectively. If the lower bound of pediatric age was increased to 1 year to match the lowest age in the XTEND-Kids, the predicted ABR for 1-<6 years age cohort was 1.28 (±2.46). The predicted ABR in pediatrics treated with 50 IU/kg BIVV001 once weekly was lower than ABR in in adult subjects with severe hemophilia A treated with 50 IU/kg Eloctate every 4 days (1.6).

The interim data of the ongoing Study EFC16295 (XTEND-kids) also supported the proposed dosage of 50 IU/kg weekly in pediatrics < 12 years. As of the data cutoff date of January 24, 2022, 82% subjects (9 out of 11) in < 6 years age cohort and 67% subjects (8 out of 12) in 6 - < 12 years age cohort had ABR of 0, the percentage which aligned with adult and adolescents (65%).

Both the interim efficacy results of Study EFC16295 (XTEND-kids) and the results RTTE model and simulation supported the proposed dose of BIVV001 (50 IU/kg once weekly) for routine prophylaxis in children with hemophilia A. Please refer to Pharmacometrics Review for detailed information.

6.4 Immunogenicity

Both FVIII inhibitor (neutralizing anti-drug antibodies, ADAs) and anti-drug antibody (ADA) were measured for immunogenicity assessment.

As of the data cut-off date, none of the study subjects developed FVIII inhibitors.

Treatment-emergent ADAs (TE ADAs) were detected in 4 out of 277 (2.2%) BIVV001 treated study subjects. All these 4 subjects were in XTEND-1 study (Study EFC16293). Three of the 4 participants had a treatment-induced and one a treatment-boosted immune response. In all 4 subjects, the ADA response was transient. Domain characterization indicated that ADAs were predominantly directed against the FVIII moiety of BIVV001 but also anti-Fc, anti-XTEN, and anti-D´D3 antibodies were detected.

Factor VIII activity profiles of the 4 subjects with TE ADAs in Study EFC16293 overlapped with subjects with ADA negative profiles and their PK parameters were comparable to the mean of ADA negative subjects. No apparent differences with respect to bleeding episodes and the PD response after BIVV001 treatment were observed in the 4 subjects with treatment-emergent ADAs compared to ADA negative subjects. Available data indicates that there's no evident impact of ADAs on FVIII PK and clinical outcomes.

6.5 Clinical Pharmacology Conclusions

BIVV001 is a recombinant fusion protein consisting of a single chain B domain deleted human FVIII covalently linked to the D'D3 domain of human VWF via the Fc domain of human immunoglobulin G1 (IgG1) and 2 XTEN polypeptides). BIVV001 is independent of endogenous VWF in order to overcome the half-life limit imposed by FVIII and VWF interactions.

General PK Profile: after administered via IV injection, the PK profile of BIVV001 exhibited a shallow distribution phase followed by a linear, and non-saturable elimination phase with a long half-life compared to other approved FVIII products. The mean terminal plasma half-life of BIVV001 was about 3.8- and 2.7-fold of the half-life of Advate (an approved FVIII product with standard half-life) and Adynovi (an approved FVIII product with extended half-life), respectively.

Dose proportionality: dose proportionality was observed for Cmax and AUC with doses ranging from 25 IU/kg to 65 IU/kg.

Steady State: weekly dosing of 50 IU/kg of BIVV001 showed minimal accumulation. With once weekly dose at 50 IU/kg, BIVV001 provided FVIII activity in the normal to near-normal range (> 40 IU/dL) for 3 to 4 days and > 10 IU/dL at the end of the weekly dosing interval in adults and adolescents. Once weekly dose of ALTUVIIIO at 50 IU/kg provided FVIII activity in the normal to near-normal range (> 40 IU/dL) for 2 to 3 days, >10 IU/dL for approximately 6 to 7 days, and in the mild hemophilia range (>5 IU/dL) at the end of the weekly dosing interval in both cohorts of children <12 years of age.

Intrinsic Factors Impacting BIVV001 PK Profiles (PK in Special Populations): Body weight was a statistically significant covariate on both clearance (CL) and volume of distribution (V). Younger children (< 12 years) with lower body weight had higher clearance, shorter half-life and lower Ctrough level of FVIII activity at steady state compared to adults and adolescents. In addition to body weight, Asian race was the only covariate that influenced the PK of BIVV001, with a higher C_{maxss}, C_{trough}, and time to 40 IU/dL FVIII activity in the Asian population compared to the non-Asian population. The PK differences between Asian and non-Asian population was not considered clinically meaningful. Other covariates (VWF antigen levels, hematocrit, blood type, and HCV/HIV status) had no impact on BIVV001 PK profiles.

PK/PD Relationships: The relationships between FVIII activity level and bleeding prevention (clinical efficacy outcome) were evaluated using a repeated time-to-event (RTTE) model. Based on FVIII PK/PD analyses, the risk of bleeding is negatively correlated with FVIII activity. Once weekly 50 IU/kg BIVV001 provided factor VIII activity levels that were associated with a low bleed risk.

Adults and Adolescents: the probability of zero bleeds in 1 year with BIVV001 50 IU/kg once-weekly regimen was predicted to be 71% (95% CI: 50%-83%) in adults and adolescents, indicating a low risk of bleed for BIVV001. The probability of first bleed in 1 year with BIVV001 50 IU/kg once weekly regimen in adults and adolescents was 35% lower compared to label-recommended regimen (standard-of-care) of Eloctate (50 IU/kg every 4 days).

Pediatrics < 12 years: the probabilities of first bleed in 1 year were predicted to be 45% [95% CI: 39%-50%] and 48% [95% CI: 42%-54%] for pediatrics 6-<12 years and <6 years,

respectively. 1.28 (±2.46). The predicted ABR in pediatrics treated with 50 IU/kg BIVV001 once weekly was 1.28, which was lower than ABR in in adult subjects with severe hemophilia A treated with 50 IU/kg Eloctate every 4 days (1.6). Additionally, despite the lower exposure, the interim efficacy results of the ongoing XTEND-Kids study showed that pediatric subjects with severe hemophilia treated with BIVV001 had a comparable annual bleeding rate (ABR) to that observed in adults and adolescents despite a reduced FVIII activity.

Above results indicates that BIVV001 the proposed dosing regimen of BIVV001 (50 IU/kg once weekly) is acceptable.

Immunogenicity: BIVV001 showed a low immunogenic potential in previously treated patients (PTPs) with hemophilia A. Inhibitor development to FVIII was not detected, and the incidence of treatment-emergent anti-drug antibodies (ADAs) was low: 4 out of 277 (2.2%) BIVV001 treated subjects developed transient ADAs. Factor VIII activity profiles of the 4 subjects with treatment emergent (TE) ADAs in Study EFC16293 overlapped with the factor VIII activity profiles of subjects with ADA negative profiles and their PK parameters were comparable to the mean of ADA negative subjects. No apparent differences with respect to bleeding episodes and the PD response after BIVV001 treatment were observed in the 4 subjects with treatment-emergent ADAs compared to ADA negative subjects. Available data indicates that there's no evident impact of ADAs on FVIII PK and clinical outcomes.

7 APPENDIX - INDIVIDUAL STUDY

7.1 Study #1 – Study 242HA101

Study Completion: 12 November 2018.

Title: A Phase 1/2a Open-Label, Dose-Escalation Study to Determine the Safety, Tolerability, and Pharmacokinetics of a Single Intravenous Injection of rFVIIIFc-VWF-XTEN (BIVV001) in Previously Treated Adults with Severe Hemophilia A. (242HA101)
Objectives: The primary objective of this study was to assess the safety and tolerability of a single Intravenous (IV) administration of BIVV001 in adult previously treated patients (PTPs) with severe hemophilia A. The secondary objective was to characterize the PK of BIVV001 after a single IV administration compared with the pharmokinetics (PK) of Advate®, with FVIII activity determined by the one-stage activated partial thromboplastin time (aPTT)-based clotting assay with Actin® FSL as activator. The exploratory objective was to characterize the PK of BIVV001 after a single IV administration compared with the PK of Advate, with FVIII activity determined by the (b) (4) chromogenic coagulation assay.
Methodology: This was a Phase 1/2a, open-label, dose-escalation, multicenter study designed to evaluate the safety, tolerability, and PK of a single IV dose of BIVV001 in PTPs with severe hemophilia A. After a brief washout (if applicable), subjects were dosed with a single IV dose of Advate followed by a PK sampling period. After another brief washout period, each subject was to be administered a single dose of BIVV001 followed by a PK sampling period. Subjects were also to undergo safety observation for 28 days following BIVV001 administration, which included inhibitor assessments 14 and 28 days after BIVV001 dosing. Two BIVV001 doses were evaluated in this study: 25 IU/kg single dose (low-dose cohort) and 65 IU/kg single dose (high-dose cohort). A step-wise dosing and dose-escalation procedure was utilized.
Number of Subjects: Planned: 18; Enrolled: 18; Treated with Advate: 16; Treated with BIVV001: 15 Evaluated: Safety: 16; Pharmacokinetics: 15
Diagnosis and Criteria for Inclusion: Adult male subjects (18 to 65 years of age) with severe hemophilia A (defined as <1 IU/dL [<1%] endogenous FVIII) who have had at least 150 exposure days (EDs) to FVIII products.
Study Treatments **Investigational medicinal product(s): BIVV001** Formulation: The drug product was provided as lyophilized material in vials, to be reconstituted with sterile water for injection at the time of dosing. Route(s) of administration: IV Dose regimen: Single dose of either 25 or 65 IU/kg **Noninvestigational medicinal product(s) (if applicable): Advate** Formulation: The drug product was provided as lyophilized material in vials, to be reconstituted with sterile water for injection at the time of dosing. Route(s) of administration: IV Dose regimen: Single dose of either 25 or 65 IU/kg
Pharmacokinetic Sampling Times FVIII activity for Advate (one-stage clotting and (b) (4) chromogenic assays) was assessed prior to the administration of Advate (predose of 25 or 65 IU/kg) and at 0.5, 1, 6, 24, 48, and 72 hours post injection. FVIII activity for BIVV001 (one-stage clotting and (b) (4) chromogenic assays) was assessed just prior to the administration of BIVV001 and at 0.17, 0.5, 1, 3, 6, 9, 24, 48, 72, 96, 120, 168, and 240 hours (10 days) post injection for all subjects administered the low dose of BIVV001 and additionally at 288 and 336 hours (14 days) post injection for those subjects administered the high dose of BIVV001 and at the EOS/ET Visit.

Pharmacokinetic Results:

- PK comparison between Advate and BIVV001 at 25 and 65 IU/kg was conducted using geometric mean for parameters and geometric mean ratios (fold change) of BIVV001 relative to Advate.
- Following Advate treatment, FVIII activity based on the one-stage clotting and chromogenic assays on Day 3 (72 hours) was 0.66% and 0.76%, respectively at 25 IU/kg and 2.33% and 3.02%, respectively at 65 IU/kg. Following BIVV001 treatment at 25 IU/kg, FVIII activity based on the one-stage clotting and chromogenic assays on Day 3 was 26.20% and 14.95%, on Day 5 (120 hours) was 12.23% and 6.93%, and on Day 7 (168 hours) was 5.32% and 3.26%, respectively. Following BIVV001 treatment at 65 IU/kg, FVIII activity based on the one-stage clotting and chromogenic assays on Day 3 was 78.21% and 43.75%, on Day 5 was 37.79% and 20.95%, and on Day 7 was 17.04% and 10.29%, respectively. Taking into account the data from both assays, FVIII activity on Day 7 after 65 IU/kg indicates Ctrough in the range of 10% to 17% with once weekly dosing with BIVV001 treatment.
- Compared to Advate treatment, FVIII activity (measured by both assays) AUC∞ was higher (p-value < 0.001) following BIVV001 treatment by 7.0- and 3.49-fold at 25 IU/kg and 6.54- and 3.99-fold at 65 IU/kg, respectively.
- FVIII activity, as measured by both assays, declined slowly following BIVV001 treatment with a t1/2 of 37.61 and 39.84 hours at 25 IU/kg and 42.54 and 45.82 hours at 65 IU/kg, respectively. Compared to Advate treatment, t1/2 was longer following BIVV001 treatment by 4.13- and 3.19-fold at 25 IU/kg and 3.24- and 3.20-fold at 65 IU/kg, respectively.
- Consistent with prolonged half-life, the time to 10% and 40% FVIII activity measured by both assays was also longer following BIVV001 treatment.
- Following Advate treatment, FVIII activity based on both assays was maintained above 10% for 23.59 and 25.16 hours, respectively at 25 IU/kg and 41.27 and 40.21 hours, respectively, at 65 IU/kg. Following Advate treatment, FVIII activity based on the one-stage clotting and chromogenic assays was maintained above 40% for 1.66 and 4.75 hours, respectively at 25 IU/kg and 19.18 and 15.95 hours, respectively, at 65 IU/kg.
- Following BIVV001 treatment, FVIII activity was maintained above FVIII activity levels of 10% and 40% over a longer period compared to Advate.
    - FVIII activity, as measured by the one stage clotting assay and the chromogenic assays was maintained above 10% for 126.10 and 92.79 hours, respectively, at 25 IU/kg and 201.58 and 168.21 hours, respectively, at 65 IU/kg.
    - FVIII activity, as measured by the one stage clotting and the chromogenic assays, was maintained above 40% for 24.89 and 16.12 hours, respectively at 25 IU/kg and 111.61 and 77.77 hours, respectively, at 65 IU/kg.

Conclusions:

Single dose of 25 or 65 IU/kg BIVV001 was well tolerated and no safety concerns were identified.
Subjects in the low-dose cohort (25 IU/kg) had an average FVIII activity level of approximately 3-5% at Day 7 after administration of BIVV001. Subjects in the high-dose cohort (65 IU/kg) had an average FVIII activity level of approximately 21% to 38% at Day 5 and approximately 10%-17% at Day 7.
FVIII activity from the one-stage clotting assay and chromogenic assay showed a terminal half-life of 37.61 and 39.84 hours for the low-dose cohort (25 IU/kg), and a terminal half-life of 42.54 and 45.82 hours for the high-dose cohort (65 IU/kg), respectively, which corresponds to a 3- to 4 fold increase compared to Advate.
Cmax from the one-stage clotting and chromogenic assays showed 161 and 141 IU/dL at 65 IU/kg, respectively, which corresponds to 0.7- to 1.2-fold difference compared to Advate. IR from the one-stage clotting and chromogenic assays of BIVV001 ranged 2 - 3 IU/dL per IU/kg at both 25 and 65 IU/kg, indicating consistent recovery across doses.
AUC∞ from the one-stage clotting and chromogenic assays showed 12800 and 8520 hr*IU/dL at 65 IU/kg, respectively, which corresponds to a 4- to 7-fold increase compared to Advate.
The predicted time to above 10% for the one-stage clotting and chromogenic assays was 201.58 and 168.21 hours at 65 IU/kg, respectively, which is longer by 4- to 5-fold compared to Advate. The predicted time to above 40% for the one-stage clottingand chromogenic assays was 111.61 and 77.77 hours at 65 IU/kg, respectively, which is longer by 5- to 6-fold compared to Advate.
The available clinical data from Study 242HA101 supports continued clinical development of BIVV001 for patients with hemophilia A.

Source: Applicant. Module 5, section 5.3 Clinical Study Reports.

7.2 Study #2 – Study 242HA102

Study Completion: 12 April 2019

Title: A Phase 1, Open-Label, Single-Site, Safety, Tolerability, and Pharmacokinetics Study of Repeat Doses of BIVV001
Objectives: The **primary objective** was to assess the safety and tolerability of a total of 4 once-weekly doses of intravenous (IV) BIVV001 at a dose of 50 IU/kg or 65 IU/kg in adult male previously treated patients (PTPs) 18 to 65 years of age (inclusive) with severe hemophilia A. The **secondary objective** was to characterize the pharmacokinetics (PK) of BIVV001 after a total of 4 once-weekly IV doses for each cohort, with factor VIII (FVIII) activity determined by the one-stage (activated partial thromboplastin time [aPTT]) clotting assay. The **exploratory objective** was to characterize the PK of BIVV001 after a total of 4 once-weekly IV doses for each cohort, with FVIII activity determined by the (b) (4) chromogenic coagulation assay.
Methodology: This was a Phase 1, open-label, single-site study to evaluate the safety, tolerability, and PK of a total of 4 once-weekly doses of 50 IU/kg or 65 IU/kg BIVV001 in adult male PTPs 18 to 65 years of age (inclusive) with severe hemophilia A who have received at least 150 exposure days (EDs) of prior FVIII treatment. The study comprised a **Screening Period**, a **Dosing Period**, and a **Safety Observation Period** as follows: **Screening Period** (approximately 21 days not to exceed 56 days): Subjects were screened for determination of eligibility. Subjects underwent a washout period prior to Screening assessments of FVIII activity and the inhibitor test. **Dosing Period** (22 days): Subjects received 4 once-weekly doses of BIVV001 on Days 1, 8, 15 and 22. During this period, subjects also underwent safety and PK assessments. A predose PK sample was taken on Day 1. In addition, there were multiple PK samples taken after dosing on Days 1 and 22, and a trough (168h) sample occurring prior to dosing on Days 8, 15, and 22. **Safety Observation Perio**d (28 days): The Safety Observation Period began on the day the subject received the last dose of BIVV001 (Day 22) and overlapped with the PK sampling period for the subject's last dose. Subjects could resume treatment with prestudy FVIII product during the 28-day Safety Observation Period after completing the Visit 16 (Day 36) activities, including the 14-day inhibitor test. For subjects who completed all 4 once-weekly doses of BIVV001, the Safety Observation Period ended with the End-of-Study Visit at Day 50. For subjects who discontinued treatment early, the Safety Observation Period ended with the Early Termination Visit 28 days after the last dose of BIVV001.
Number of Subjects: Planned: up to 25 subjects (10 subjects in the 50 IU/kg cohort and up to 15 subjects in the 65 IU/kg cohort) Enrolled: 24 subjects (10 subjects in the 50 IU/kg cohort and 14 subjects in the 65 IU/kg cohort) Treated: 24 subjects (10 subjects in the 50 IU/kg cohort and 14 subjects in the 65 IU/kg cohort) Evaluated: Safety: 24 subjects (10 subjects in the 50 IU/kg cohort and 14 subjects in the 65 IU/kg cohort) Pharmacokinetics: 23 subjects (9 subjects in the 50 IU/kg cohort and 14 subjects in the 65 IU/kg cohort)
Diagnosis and Criteria for Inclusion: Adult male PTPs 18 to 65 years of age (inclusive) with severe hemophilia A who have received at least 150 EDs of prior FVIII treatment.
Study Treatments **Investigational medicinal product(s): BIVV001** Formulation: lyophilized powder in a sterile vial that requires reconstitution with Sterile Water for Injection (diluent) at the time of dosing. Each vial of drug product included 1000 IU of BIVV001 along with the following excipients: L histidine, L arginine hydrochloride, sucrose, calcium chloride dihydrate, polysorbate 80, (b) (4) (b) (4)

Route(s) of administration: IV
Dose regimen: 4 once-weekly doses at 50 IU/kg or 65 IU/kg
Noninvestigational medicinal product(s)
Not applicable):

Pharmacokinetic/Pharmacodynamic Sampling Times and Bioanalytical Methods:
FVIII activity was assessed using a one-stage (aPTT-based) clotting and (b) (4) chromogenic coagulation assays.
The PK sampling schedule was as follows:

- Day 1: PK assessments occurred pre-dose and at the following post-dose timepoints: 30 (±3) minutes, 3 hours (±15 minutes), 24 hours (±1 hour), 48 hours (±2 hours), 72 hours (±2 hours), and 120 hours (±2 hours).
- Day 8: PK assessment occurred pre-dose and served as the Day 1 168 hours timepoint.
- Day 15: PK assessment occurred pre-dose and served as the Day 8 168 hours timepoint.
- Day 22: PK assessments occurred pre-dose (Day 15 168 hours timepoint) and at the following post-dose timepoints: 30 (±3) minutes, 3 hours (±15 minutes), 24 hours (±1 hour), 48 hours (±2 hours), 72 hours (±2 hours), 120 hours (±2 hours), 168 hours (±5 hours), 240 hours (±5 hours), and 336 hours (±5 hours)

Pharmacokinetic Results:

- The mean FVIII activity profiles on Day 22 were comparable to Day 1 following once-weekly BIVV001 treatment at both 50 and 65 IU/kg supporting minimal accumulation.
- On Day 22 following once-weekly 50 IU/kg BIVV001 treatment, the mean FVIII activity was 46.28% and 30.46% at 72 hour; 22.30% and 14.48% at 120 hour; and 9.83% and 6.74% at 168 hour with the one-stage clotting and chromogenic assay, respectively.
- On Day 22 following once-weekly 65 IU/kg BIVV001 treatment, the mean FVIII activity was 69.31% and 37.63% at 72 hour; 27.21% and 16.51% at 120 hour; and 11.81% and 7.64% at 168 hour with the one-stage clotting and chromogenic assay, respectively.
- The geometric mean t1/2 based on one-stage clotting and chromogenic assays, respectively, was 41.25 and 43.87 hour following 50 IU/kg; and 37.31 and 42.51 hour following 65 IU/kg.
- On Day 22 following once-weekly 50 IU/kg BIVV001 treatment, the geometric mean Cmax was 131 and 115 IU/dL; the geometric mean IR was 2.43 and 2.15 IU/dL per IU/kg; the geometric mean AUC0-tau was 8290 and 5860 hr*IU/dL with one-stage clotting and chromogenic assay, respectively.
- On Day 22 following once-weekly 65 IU/kg BIVV001 treatment, the geometric mean Cmax was 171 and 172 IU/dL; the geometric mean IR was 2.45 and 2.52 IU/dL per IU/kg; the geometric mean AUC0-tau was 11200 and 7870 hr*IU/dL with one-stage clotting and chromogenic assay, respectively.
- The Cmax and IR for one-stage and chromogenic assays were comparable on Days 1 and 22 indicating consistent recovery within dose level (50 and 65 IU/kg once-weekly treatment).
- The AI for one-stage and chromogenic assays at steady state was close to unity. The one-stage and chromogenic FVIII activity AI at steady state was 1.07 and 1.08, respectively at 50 IU/kg; and 1.05 and 1.07, respectively at 65 IU/kg.
- Across the 50 and 65 IU/kg dose levels, the one-stage and chromogenic FVIII activity dose-normalized AUC0-tau was comparable supporting dose proportionality in AUC0-tau with once-weekly dosing.
- The geometric mean Cavg was >35% with 50 IU/kg once-weekly dosing; and >47% with 65 IU/kg once-weekly dosing.
- The geometric mean Ctrough of one-stage and chromogenic assay FVIII activity at steady state was 9.16 and 6.51 IU/dL with 50 IU/kg once-weekly dosing, respectively; and 10.8 and 7.37 IU/dL with 65 IU/kg once-weekly dosing, respectively.
- On Day 22, the geometric mean one-stage and chromogenic FVIII activity was maintained above 40% for 76.18 and 55.84 hour, respectively at 50 IU/kg; and 91.87 and 68.92 hour, respectively at 65 IU/kg.
- On Day 22, the geometric mean one-stage and chromogenic FVIII activity was maintained above 10% for 162.75 and 141.16 hour, respectively at 50 IU/kg; and 172.53 and 146.70 hour, respectively at 65 IU/kg.

Conclusions: Repeat doses of BIVV001 were well tolerated and no safety concerns were identified. No inhibitor development to FVIII was detected and there were no reports of hypersensitivity, anaphylaxis, or vascular thrombotic events. After the weekly 50 IU/kg dose, mean steady state FVIII activity levels 3, 5 and 7 days following drug administration were 46%, 22%, and 10%, respectively (one-stage clotting assay). After the weekly 65 IU/kg dose mean steady state FVIII activity levels 3, 5, and 7 days following drug administration were 69%, 27% and 12%, respectively (one-stage clotting assay). The Cmax and IR for one-stage and chromogenic assays were comparable on Days 1 and 22 indicating consistent recovery within dose level (50 and 65 IU/kg once-weekly treatment). On Day 22 with once-weekly dosing, the one-stage and chromogenic FVIII activity was maintained above 10% for 163 and 141 hour, respectively at 50 IU/kg; and 173 and 147 hour, respectively at 65 IU/kg. The results of this study confirm a prolonged t1/2 of BIVV001, between 37-44 hours, with minimal accumulation for weekly dosing regimens of 50 IU/kg and 65 IU/kg. The available clinical data from Study 242HA102 support continued clinical development of BIVV001 in treatment of patients with hemophilia A.

Source: Applicant. Module 5, section 5.3 Clinical Study Reports.

7.3 Study #3 – Study PKM 17085

Study Completion Date: 24 November 2021

Title: A Phase 1, Single-Site, Open-Label Study to Assess Pharmacokinetics of efanesoctocog alfa (BIVV001), Standard Half-Life and Extended Half-Life FVIII after each Single Intravenous Injection in a Fixed Sequence, in Previously Treated Adults with Severe Hemophilia A
Objectives: The primary objective is to assess the half-life of BIVV001, SHL rFVIII and EHL rFVIII after a single intravenous (IV) injection. The secondary objectives are 1) to characterize additional PK parameters of BIVV001, SHL rFVIII and EHL rFVIII after a single IV injection; and 2) to evaluate the safety and tolerability of a single IV injection of BIVV001
Methodology: This was a Phase 1, single-center, single-arm, nonrandomized, open-label, 3-period, fixed sequence, PK comparison study assessing the PK profiles of BIVV001, SHL and EHL rFVIII after a single IV injection in previously treated patients with severe hemophilia A.
Number of Subjects: Planned: 12; Screened: 14; Enrolled: 13 Safety: 13; Pharmacokinetic: 13; Immunogenicity (anti-drug antibody, ADA): 13
Diagnosis and Criteria for Inclusion: Participants were male; 18 to 65 years of age (inclusive) at the time of informed consent; with documented severe hemophilia A (defined as < 1 IU/dL [< 1%] endogenous FVIII) with prior treatment, of at least 150 days, with any recombinant and/or plasma-derived FVIII and/or cryoprecipitate products; and a platelet count of ≥100 000 cells/µL at Screening.
Study Treatments **Investigational medicinal product(s):** **BIVV001** Formulation: lyophilized powder in a sterile vial (1000 IU) that requires reconstitution with sterile water for injection (diluent). **Full length recombinant coagulation factor VIII (Advate®)** Formulation: lyophilized powder in single-use vials containing 1000 IU. It comes with 2 mL of sterile water for injection (included in the commercial package) **Antihemophilic factor (recombinant), PEGylated (Adynovi®)** Formulation: lyophilized powder in single-use vials containing 1000 IU. The solvent vial contains 2 mL of sterile water for injections (included in the commercial package) Route(s) of administration: IV

Dose regimen: a single dose of 50 IU/kg for each study intervention
Results: Pharmacokinetics As presented in Figure 5, BIVV001 maintained a mean FVIII activity level > 40 IU/dL up to 96 hours (4 days) whereas Advate and Adynovi maintained up to 6 hours (< 1 day) and up to 24 hours (1 day), respectively. BIVV001 maintained a mean FVIII activity level >10 IU/dL approximately up to 168 hours (7 days) whereas Advate and Adynovi maintained up to 24 hours (1 day) and up to 48 hours (2 days), respectively. BIVV001 maintained a mean FVIII activity level >1 IU/dL up to 288 hours (12 days) whereas Advate and Adynovi maintained up to 72 hours (3 days) and up to 120 hours (5 days), respectively. Following a single 50 IU/kg IV dose of Advate, Adynovi, and BIVV001, the median tmax of the baseline-corrected FVIII activity generally occurred at the first collected sample (0.17 hours postdose) across all participants and treatments (range 0.17 to 1.00 hours) (Table 5). The Cmax and IR values indicated consistent recovery across the 3 FVIII products. A single 50 IU/kg dose of BIVV001 exhibited reduced CL (0.17- and 0.28-fold), which resulted in a longer t1/2z (3.94 -and 2.82-fold) and a higher exposure (AUC, 6.03- and 3.57-fold) compared with Advate and Adynovi, respectively.
Conclusions: • Following a single 50 IU/kg IV dose, BIVV001 exhibited an approximately 3- to 4-fold longer mean t1/2z (44.4 hours) compared with Adynovi (16.3 hours) and Advate (11.7 hours), respectively, based on FVIII activity levels measured by a one-stage aPTT assay. • BIVV001 maintained a mean FVIII activity level >40 IU/dL up to 4 days postdose, whereas Advate and Adynovi maintained up to 1 day postdose. BIVV001 also maintained a mean FVIII activity level >10 IU/dL up to nearly 7 days postdose, whereas Advate and Adynovi maintained up to 1 and 2 days postdose, respectively. • A single dose of BIVV001 was well tolerated and no safety concerns were identified.

Source: Applicant. Module 5, section 5.3 Clinical Study Reports.

7.4 Study #4 – Study EFC16293

Study Completion Date: 03 February 2022

Title: A Phase 3 Open-Label, Multicenter Study of the Safety, Efficacy, and Pharmacokinetics of Intravenous Recombinant Coagulation Factor VIII Fc-von Willebrand Factor-XTEN Fusion Protein (rFVIIIFc-VWF-XTEN; BIVV001) in Previously Treated Patients ≥12 Years of Age With Severe Hemophilia A
Objectives: The primary objective is to evaluate the efficacy of BIVV001 as a prophylaxis treatment. The pharmacokinetic objective (one of the secondary objectives) is to assess the PK of BIVV001 based on the one-stage activated partial thromboplastin time (aPTT) and (b) (4) chromogenic FVIII activity assays.
Methodology: This Phase 3 open-label study was comprised of 2 arms: Arm A and Arm B. Participants who were on a prophylaxis treatment regimen with FVIII prior to the study entered Arm A and received BIVV001 50 IU/kg IV once weekly for up to 52 weeks. The majority of study participants enrolled in Arm A had previously completed study OBS16221 (an observational study of patients receiving a marketed FVIII replacement therapy for up to 12 months). Participants who were on an on-demand treatment regimen prior to the study entered Arm B and received BIVV001 50 IU/kg IV as on-demand treatment of bleeding episodes for 26 weeks before switching to BIVV001 50 IU/kg IV once weekly as a prophylaxis treatment regimen for another 26 weeks. PK assessments at Day 1 were performed after a washout period of at least 4 to 5 days, depending on prior FVIII therapy. At least 16 participants in Arm A at selected sites were included in the Sequential PK subgroup and underwent PK sampling over 2 weeks (336 hours) after the first dose of BIVV001 (Baseline) and again at Week 26 (study drug was withheld on Week 2 and Week 27 to allow for this sampling). All other participants underwent abbreviated PK sampling at Baseline up to 7 days (168 hours). In addition, peak and trough FVIII measurements was performed in all participants throughout the study.

FVIII activities were measured using WHO plasma standard with the aPTT-based one-stage clotting (OSC) assay as the primary evaluation of PK endpoints. The lower limit of quantification (LLOQ) for one stage clotting assay was 1 IU/dL.
Participants from either arm who had major surgery after the first dose of BIVV001 were included in the surgery subgroup. A minimum of 10 major surgeries in at least 5 patients was targeted to assess the control and prevention of bleeding during use of BIVV001 in the surgical setting.

Number of Subjects:
Planned: ~ 150 (Arm A: 124, Arm B: 26); Completed: 159
Analyzed:
Efficacy (Full Analysis Set [FAS]): Arm A: 133; Arm B on-demand: 26; Arm B prophylaxis: 26
Safety (Safety Analysis Set): Arm A: 133; Arm B on-demand: 26; Arm B prophylaxis: 26
Pharmacokinetics:
PK analysis Set (PKAS): Arm A: 133; Arm B on-demand: 26; Arm B prophylaxis: 26
Sequential PK subgroup: 17 (Arm A)
Surgery: 13 (overall)

Diagnosis and Criteria for Inclusion and Exclusion:
Participants enrolled in this study were previously treated patients (PTPs) with severe hemophilia A (defined as <1 IU/dL [<1%] endogenous FVIII or a documented genotype known to produce severe hemophilia A), aged 12 years or older. In addition, participants from Arm B (on-demand regimen) had to have at least 12 bleeding episodes in the previous 12 months or at least 6 bleeding episodes in the previous 6 months prior to study enrollment. Previous treatment for hemophilia A (prophylaxis or on-demand regimen) was defined as any treatment with any recombinant and/or plasma derived FVIII, or cryoprecipitate for at least 150 EDs. Participants with a history of a positive inhibitor test or with a positive inhibitor test result at screening were excluded.

Study Treatments
Investigational medicinal product(s):
BIVV001
Formulation: lyophilized powder in a sterile vial (1000 IU) that requires reconstitution with sterile water for injection (diluent).
Route(s) of administration: IV
Dose regimen:
• Arm A: prophylactic treatment regimen with once weekly injection of 50 IU/kg BIVV001 for 52 weeks
• Arm B: on-demand regimen with BIVV001 for 26 weeks followed by prophylactic treatment regimen with once weekly injection of 50 IU/kg BIVV001 for 26 weeks All bleeding episodes (during either prophylaxis or on-demand treatment regimen) were to be treated with a single dose of 50 IU/kg BIVV001 (on clinical indication additional 30 or 50 IU/kg doses every 2-3 days could be administered). All participants undergoing minor or major surgery were to receive a pre-operative loading dose of 50 IU/kg, followed by additional 30 or 50 IU/kg doses every 2-3 days on clinical indication.

Results: Pharmacokinetics
• A single BIVV001 dose of 50 IU/kg resulted in mean FVIII activities in the normal to near-normal range (>40 IU/dL) for 3 to 4 days and mean FVIII activity of 11.92 IU/dL at the end of the 7-day dosing interval.
• After a 50 IU/kg of BIVV001, the majority of participants showed peak FVIII activities (mean Cmax 131 IU/dL) below the upper physiological limit of 150 IU/dL.
• The mean (SD) half-life of BIVV001 was 47.6 (8.86) hours and the mean (SD) incremental recovery (IR) was 2.60 (0.648).
• Once weekly 50 IU/kg regimen showed minimal accumulation (mean accumulation index: 1.17).
• An effect of age on PK was observed with slightly lower AUC and half-life in adolescents as compared to adults.
• Four participants had transient treatment-emergent ADAs with no effect on peak and trough FVIII activity levels.

Conclusions:
This study demonstrated that weekly BIVV001 prophylaxis demonstrated highly effective protection against bleeds and superiority to prior prophylactic FVIII replacement therapy, with a statistically significant reduction in ABR based on intra-patient comparison, in adult and adolescent PTPs with severe hemophilia A. Also, it confirmed that BIVV001 provided high sustained factor activity levels in the normal to near normal range for the majority of the week with once weekly administration. In addition, BIVV001 prophylaxis demonstrated a

significant improvement in physical health, pain intensity and joint health. Inhibitor development to FVIII was not detected and reported TEAEs were generally consistent with what is anticipated in an adult and adolescent population with severe hemophilia A.

Source: Applicant. Module 5, section 5.3 Clinical Study Reports.

7.5 Study #5 – Study EFC16295

Interim data cut-off Date: 24 January 2022

Title: A Phase 3 open-label, multicenter study of the safety, efficacy and pharmacokinetics of intravenous recombinant coagulation Factor VIII Fc-von Willebrand Factor-XTEN fusion protein (rFVIIIFc-VWF-XTEN; BIVV001) in previously treated pediatric patients <12 years of age with severe hemophilia A
Objectives: The primary objective is to evaluate the safety of BIVV001 in previously treated pediatric participants with hemophilia A The pharmacokinetic objective (one of the secondary objectives) is to assess the PK of BIVV001 based on the one-stage activated partial thromboplastin time (aPTT) and (b) (4) chromogenic FVIII activity assays.
Methodology: This is a multinational, multicenter, single-arm, open-label Phase 3 study of the safety, efficacy, and pharmacokinetics (PK) of IV administered BIVV001 in previously treated patients (PTPs) <12 years of age with severe hemophilia A (defined as <1 IU/dL [<1%] endogenous FVIII or a documented genotype known to produce severe hemophilia A). The study is comprised of 2 age cohorts of children (<6 years and 6 to <12 years), and participants were to receive BIVV001 at a dose of 50 IU/kg IV once weekly for 52 weeks. Pharmacokinetic assessments at Baseline (Day 1) were performed after a washout period of at least 3 to 4 days depending on age. At least 12 participants in each age cohort were to be included in the PK subgroup, undergoing PK sampling after their first dose of BIVV001 at Baseline (Day 1) up to 7 days (168 hours). In addition, peak and trough FVIII sampling was performed in all participants throughout the study. FVIII activities were measured using the aPTT-based one-stage clotting (OSC) assay, as the primary evaluation of PK endpoints. Participants who undergo major surgery during the study were to be included in the surgery subgroup. Definitions for major surgery were defined in the study protocol. An independent external Data Monitoring Committee (DMC) is responsible for evaluating and monitoring the safety and tolerability of BIVV001 on an ongoing basis during the study.
Number of Subjects: Planned: ~ 65 participants to achieve at least 50 participants with at least 50 exposure days (Eds) • 25 participants <6 years of age, at least 12 in the PK subgroup • 25 participants 6 to <12 years of age, at least 12 in the PK subgroup **Number of participants analyzed at the interim data cut-off:** Efficacy (Full Analysis Set [FAS]): overall: 67; age cohort <6 years: 31; age cohort 6 to <12 years: 36 Full Analysis Set with an efficacy period: 63; age cohort <6 years: 27; age cohort 6 to <12 years: 36 Safety (Safety Analysis Set): overall: 67; age cohort <6 years: 31; age cohort 6 to <12 years: 36 **Pharmacokinetics:** overall: 32; age cohort <6 years: 14; age cohort 6 to <12 years: 18 Surgery Subgroup: overall: 32; age cohort < 6 years: 1; age cohort 6 to <12 years: 0)

Diagnosis and Criteria for Inclusion and Exclusion: Participants enrolled in this study were PTPs with severe hemophilia A (defined as <1 IU/dL [<1%] endogenous FVIII), younger than 12 years of age. Previous treatment of hemophilia A was defined as any treatment with any recombinant and/or plasma derived FVIII, or cryoprecipitate for at least 150 EDs for patients aged 6-11 years and for at least 50 EDs for patients aged <6 years. Participants with a history of a positive inhibitor test or with a positive inhibitor test result at Screening were excluded.
Study Treatments **Investigational medicinal product(s): BIVV001** Formulation: lyophilized powder in a sterile vial (1000 IU) that requires reconstitution with sterile water for injection (diluent). Route(s) of administration: IV Dose regimen: once weekly injection of 50 IU/kg
Results: Pharmacokinetics (Interim) • A single BIVV001 dose of 50 IU/kg resulted in mean FVIII activities in the normal to near-normal range (>40%) for 2 to 3 days, with mean (SD) FVIII activity, based on OSC assay, of 6.93 (1.76) IU/dL and 5.84 (1.73) IU/dL in 6 to <12 years and <6 years of age cohorts, respectively at the end of the 7-day dosing interval. • The mean (SD) Cmax was 125 (47.4) IU/dL. The majority of participants maintained Cmax within upper physiological limit of 150 IU/dL, while indicating a consistent recovery across study duration. • The mean (SD) terminal half-life of BIVV001 was 42.4 (3.70) hours and 39.9 (5.71) hours in 6 to <12 years and <6 years of age cohorts, respectively. • There were no participants with a treatment emergent ADA response (ie, treatment boosted or treatment-induced ADAs). .
Conclusions: The interim results from this study show that once weekly BIVV001 50 IU/kg IV was well tolerated and effective as routine prophylactic to protect against bleeding episodes in previously treated patients <12 years of age with severe hemophilia A. In addition, BIVV001 was effective for the control of bleeding episodes and provided hemostatic efficacy during a surgical procedure. Inhibitor development to FVIII was not detected. BIVV001 PK showed high sustained FVIII activity throughout the 7-day dosing interval. Overall, available data support the use of BIVV001 in pediatric patients with hemophilia A.

Source: Applicant. Module 5, section 5.3 Clinical Study Reports.